FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DO MESTRADO INTEGRADO EM MEDICINA

DANIELA JARDIM PEREIRA

INTEGRATING PIECES IN AUTISM SPECTRUM DISORDERS: THE WEAK CENTRAL COHERENCE ACCOUNT

ÁREA DAS NEUROCIÊNCIAS

TRABALHO REALIZADO SOBRE A ORIENTAÇÃO DE:

PROFESSOR DOUTOR MIGUEL CASTELO-BRANCO

PROFESSORA DOUTORA PAULA TAVARES

MARÇO 2010

TABLE OF CONTENTS

ABSTRACT 1

RESUMO 2

ABBREVIATIONS 4

INTRODUCTION: THE ASD PUZZLE 6

LINKING THE WCC ACCOUNT WITH OTHER THEORIES 10

1. THE MOST INFLUENTIAL COGNITIVE THEORIES 10
   - a) Theory of Mind and WCC 10
   - b) Executive Dysfunction and WCC 12
2. OTHER THEORIES 14
   - a) Enhanced Perceptual Functioning model 15
   - b) Underconnectivity theory 18
   - c) Empathizing-Systematizing (E-S) 20

THE VISUAL PIECE TO COHERENCE 22

1. VISUAL PROCESSING 23
2. PSYCHOPHYSICAL, BEHAVIOURAL AND CLINICAL STUDIES 26
   - a) Block Design Test 26
   - b) Embedded Figures Test 29
   - c) Visual Illusions 30
   - d) Navon Figures Test 32
   - e) Achieving the “whole”: Impossible Figures, Fragmented Figures and Drawings 35
   - f) Visual Motion 37
   - g) Face Processing 42

3. ELECTROPHYSIOLOGICAL STUDIES 46
4. IMAGING STUDIES 50

DISCUSSION 58

CONCLUSION 63

ACKNOWLEDGEMENTS 63

REFERENCES 64

ABSTRACT

Introduction: Autism spectrum disorders are characterized by both social and non-social impairments, namely a triadic core of deficits in the social, communication and behavioural domains along with some strengths in perceptual functioning and the manifestation of "islets of abilities". The weak central coherence account provides an explanatory model for the islets of perceptual competence and the tendency for detail and local processing in individuals with autism, as well as for some of the non-triadic features. A local processing *bias*, with inability to extract the gestalt, does therefore seem to be present in autistic individuals. *Objectives:* In this paper, we aim to review scientific evidence in favor of the weak central coherence in the visual processing domain and the position of this account in recent autism investigation in relation with other relevant theories. *Scope of the discussion:* Considerable evidence supporting weak central coherence account has been gathered by psychophysical, behavioral, clinical, electrophysiological and imaging studies; although findings are not consensual. We discuss the interpretation of these findings and methodological limitations that might contribute to diverging results. Additionally, we argue about the inadequacy of a single etiological model to explain autism in the light of current studies. *Conclusion:* An outstanding question remains: can a global perceptual deficit be identified in autism or can just a matter of a distinct cognitive style be invoked? Further research is needed to clarify the specificity and universality of weak central coherence in autism, as well as the underlying neurobiological mechanisms.

Key words: weak central coherence, autism spectrum disorders, visual processing.

RESUMO

Introdução: As perturbações do espectro autista são caracterizadas por uma tríade central de défices na comunicação, no comportamento e no domínio social, em conjunto com capacidades superiores no funcionamento perceptivo, identificando-se, por vezes, verdadeiras "ilhas de conhecimento". A Teoria da Coerência Central oferece um modelo explicativo para as "ilhas" de competências perceptivas, em particular a tendência para o detalhe e processamento local, e ainda para algumas das características não integradas na tríade autista. De facto, os indivíduos autistas parecem apresentar uma propensão para o processamento local, em conjunto com uma incapacidade de extrair o significado global de um estímulo. *Objectivos:* Este artigo consiste numa revisão de diversos estudos científicos, na área das neurociências, que abordam a Teoria da Coerência Central no espectro autista, com especial enfoque no processamento visual. Pretendemos, igualmente, debater a contribuição desta teoria para investigação actual nos grupos autistas e determinar a sua relação com as hipóteses cognitivas ou biológicas mais proeminentes. *Desenvolvimento:* Vários estudos psicofísicos, comportamentais, clínicos, electrofisiológicos e imagiológicos têm vindo a demonstrar a presença de fraca coerência central nos indivíduos autistas; no entanto, as evidências científicas relativamente a este aspecto são ainda controversas e contraditórias. Discutimos a interpretação destes resultados divergentes e o papel de possíveis limitações metodológicas. Consideramos também, à luz da investigação científica actual, a possibilidade de se abandonar a procura de uma única causa explicativa. *Conclusão:* Permanece, assim, uma questão relevante: estará presente um défice perceptivo global nos indivíduos autistas ou deveremos antes evocar um estilo cognitivo simplesmente distinto? Efectivamente, é necessária investigação adicional para que se possa compreender claramente a especificidade e universalidade da Teoria da Coerência Central no autismo, bem como os mecanismos neurobiológicos subjacentes.

Palavras-chave: fraca coerência central, perturbações do espectro autista, processamento visual

ABBREVIATIONS

ADOS - autism diagnostic observation schedule

ASD - autism spectrum disorders

BD - block design

CC - central coherence

CEFT - children's embedded figures test

CPA - complete probe advantage

DSM-IV-TR - diagnostic and statistical manual of mental disorders - fourth Edition - text revision

DTI - diffusion tensor imaging

ED - executive dysfunction

EF - executive functions

EFP - enhanced perceptual functionning

EFT - Embedded Figures test

ERP - event related potentials

E-S - empathizing-systematizing

FA - fractional anisotropy

FCS - flicker contrast sensitivity

FFA - fusiform face area

fMRI - functional magnetic resonance imaging

GDM - global dot motion task

HFA - high functioning autism

HFA - NP - HFA individuals without a BD peak

HFA - P - HFA individuals with a BD peak

IOG - inferior occipital gyrus

LFA - low functioning autism

LGN - lateral geniculate nucleus

LIFG - left inferior frontal gyrus

LSTG- left superior temporal gyrus

MOG - medial occipital gyrus

MR - magnetic resonance

PC - perceptual cohesiveness

PDD-NOS - pervasive developmental disorder - not otherwise specified

PLDs - pointing light displays

PMLS - postero-medial bank of lateral suprasylvian sulcus

RF - receptor field

TD - tipically developing individuals

TD-P - tipically developing individuals with a BD peak

ToM - Theory of Mind

UT - underconnectivity theory

VBM - voxel based morphometry

WCC - weak central coherence

WISC - Wechsler intelligence scales for children

A review of the literature was performed utilizing Pubmed, B-on and similar search engines such Science Direct using the following key words: weak central coherence, underconnectivity theory, ERP +autism+visual+perception, fMRI+local+autism, fMRI+autism+face processing, DTI+autism. Articles cited are limited to those we consider the classic papers or the ones including the best series on the subject.

INTRODUCTION: THE ASD PUZZLE

Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by the symptomatic triad: deficits in social interaction, deficits in communication and restricted/stereotyped pattern of behavior, interests and activities (DSM-IV- TR, APA, 1994). In addition to these features, other clinical aspects are present in many autistic children as: sensory abnormalities (with a prevalence higher than 90% in autism, 80% in Asperger and variable in PDD-NOS), developmental regression, motor signs, sleep disturbance, gastrointestinal disturbance, epilepsy and co-morbid psychiatric diagnosis (Geschwind, 2009). At a more cognitive level, obsessive pursuit of particular interests and "islets of ability" have also been described and considered specific features of ASD, although not being universal (Frith, 2003). It is not surprising that several theories have been proposed to explain this complex pattern of specific manifestations, and in particular the main triad of deficits that characterize individuals with ASD. These theories include the Theory of Mind (ToM) and the Executive Dysfunction (ED) accounts. The Theory of Mind (ToM) model postulates that autistic subjects have difficulties in conceptualizing mental activity in others as well as in attributing intention to and predicting the behavior of others. The Executive Dysfunction (ED) model highlights impairment in a broad range of functions such as planning, working memory, impulse control, inhibition and mental flexibility. Aspects related to the initiation and monitoring of action have also been invoked, but the detailed research on the subcomponents of the executive system in autism is beyond the scope of this review.

Despite providing important insights of the three core impairments, these accounts have in general failed to explain the apparent strengths of ASD, such as good visuospatial ability, enhanced rote memory, putative savant talent and uneven IQ test patterns (typically with best performance in the Block Design (BD) subtest and the poorest in the Comprehension subtest).

To explain this ASD puzzle composed of both weaknesses and strengths, Frith in her book of 1989, revised in 2003 (Frith, 2003), proposed that individuals with autism may have a "specific imbalance in integration of information at different levels" (p.121, Frith and Happé, 1994). In other words, non autistic individuals tend to process information in a global way, integrating fragments to form a consistent and meaningful unit. Frith named "central coherence" this tendency of normal information processing. In this way, individuals with ASD would have a "weak central coherence" (WCC) as they tend to use a "piece-meal processing" strategy, that is, a preference for processing parts over wholes, resulting in a relative inability to extract global form (Frith and Happé, 1994). This could explain some of the non-triad features and good performance in tasks where a superior local processing is advantageous. Classic examples of the possible advantages of focused local processing are the Block Design test (BD) and Children's Embedded Figures test (EFT).

Consequently, in the past two decades, several studies did attempt to find evidence of weak central coherence in ASD. In the visual-spatial domain, besides BD and EFT, researchers have been studying performance in tasks involving hierarchical figures, visual illusions, face perception, drawing (constructive) abilities, motion coherence, visual search and others, which will be discussed to a great extent in this article. Verbal impact of local processing has also been investigated with special relevance to homograph reading test, sentence completion/gap tests and tasks using ambiguous sentences (Happé and Frith, 2006; Happé and Booth, 2008). Moreover, "piecemeal processing" across multiple high level cognitive domains may be the subjacent cause of echolalia, pronoun reversal, neologisms and metaphorical expressions characteristic of ASD, as reviewed by Noens and van Berckelaer-Onnes (2005). However, this explanatory link still remains speculative.

In the auditory modality, absolute pitch, superior pitch discrimination and memory have been described as significantly more common among the autistic population (Heaton et al, 1998, 2003, 2008 cited by Happé and Frith, 2006). In recent years the study of WCC has departed from pure behavioral studies to incorporate also neuroimaging studies, which have the potential to provide further insight about the underlying neurological mechanisms of WCC. Two general neurobiological hypotheses, that have also been posed to explain other neurodevelopmental disorders, can be considered to possibly underlie WCC: deficits in a specific neural pathway or brain region and diffuse changes in neural connectivity (Ke et al, 2009). It remains to be understood how these novel techniques will help explain the complex cognitive phenotype in ASD.

Recent research on the WCC account has lead to modifications on Frith's original concept. First, the tendency to focus on partial information rather than global processing has been considered a "cognitive style" or a processing *bias* more than a real inability in global processing. This approach gives the perception of autism as a continuum, being the extreme end of a distribution of cognitive styles in the general population (Happé and Frith, 2006). Thus, a person with weak coherence is actually able to extract the global gist if required to, such as when a cue is given. Second, reduced global processing may be a consequence of superior local processing, instead of a deficit by itself. Hence, according to Happé and Booth (2008) weak coherence is considered as "the result of two separable dimensions – reduced tendency to integrate information and increased tendency to featural processing" (p.160). The separability of these two dimensions (local vs. global processing) is suggested by researchers even for typical development. Finally, the third aspect of the original concept that as changed is that weak coherence is no longer considered a central cause of the three core impairments of ASD, but rather an alongside epiphenomenon which may not be necessarily related with social-cognitive deficits (Frith, 2003; Happé and Frith, 2006; Happé and Booth, 2008). This new approach, assumes the symptomatic triad as being "fractionable", with social and non-social aspects of ASD having distinct causes (Happé and Ronald, 2008). Genetic studies also point in this direction, considering that ASD may reflect a combination of heritable cognitive-behavioral components (endophenotypes) (Geschwind, 2009). Furthermore, the idea of distinct causes for ASD symptoms has lead to an increased interest in the relation between main cognitive theories and neurobiological research.

Therefore, we begin our revision by discussing the links between WCC and other theories trying to explain the puzzling features of ASD. Overlapping points with WCC and different contributions of each theory will be then explored. In the second part of this paper, we will focus only on the WCC account and its related evidence specifically in the visual domain, as we consider this to be the most productive area of investigation approaching WCC. We review psychophysical, behavioural, clinical, electrophysiological and imaging studies. Finally, we proceed to a comprehensive discussion of the most important aspects reviewed and analyze the clinical and therapeutic impact of those findings.

LINKING THE WCC ACCOUNT WITH OTHER THEORIES

Since Kanner's (1943) first description of autism, research in this area has broadened considerably, including the genetic, cognitive and neural levels. Accordingly, several theories of ASD have emerged and some attempts to provide unifying links between them have been established. The WCC as a prominent theory, has been studied in comparison to other major cognitive theories (ToM and EF). A current challenge is to look for similarities and to find out whether these theories can be interpreted as different pieces of the same puzzle. On the other hand, some researchers have brought to light new hypotheses and parallel accounts, which offer a new approach of the WCC, motivated by the acquisition of new knowledge on brain function, as measured by modern techniques.

1. THE MOST INFLUENTIAL COGNITIVE THEORIES

a) Theory of Mind and WCC

This term, first defined in 1978 by Premack and Woodruff, means the capacity to predict other mental states, which implies a second-order representation. The expression "theory of mind" was then adopted by Baron-Cohen et al (1985) in a study with autistic, Down's syndrome and normal children, in which they examine a lack of this theory in the first group using the well known "Sally-Anne experiment". Not knowing what "other people know, want, feel or believe" (Baron-Cohen et al, 1985) is a major obstacle to normal social interaction, including verbal and non-verbal communication. This also suggests why ToM deficit is one of the most tested and widely accepted theories in ASD, with extensive behavioural evidence for a deficit in mentalizing (Hill and Frith, 2003). One has however to take into account that ToM is a phenomenological theory and that its links to brain physiology remain widely disputed. Neuroimaging studies are playing a crucial role in quest to understand the neural mechanisms underlying impairment of the ToM system in autism (for a review on this issue see Frith & Frith, 2003; Hill & Frith, 2003; Baron-Cohen & Belmonte, 2005).

However, one of the main weaknesses of this account is that it cannot explain the restricted/stereotyped pattern and non-triadic features of autism. This has been claimed to be precisely the strength of WCC. Indeed, many researchers started to approach both theories as distinct contributions to explain distinct features, rather than alternative and divergent accounts for ASD. In a study where performance in first and second order belief tasks, BD, visual illusions and ambiguous figures were tested, Best et al (2008) concluded that measures of ToM, WCC and ED "contribute additively to discriminating the SCQ [Social Communication Questionnaire] status of participants"(p.844).

Frith, in the second edition of her book (2003), suggested that the initial theory should be revised when considering the assumption that weak coherence, as a core deficit, may also explain theory of mind impairment, preventing the acquisition of mentalizing. In the attempt to explain why some people with autism are able to "learn" about others mental states (conscious mentalizing), she considered new alternatives: first, mentalizing may not require large integration of information; second, a small proportion of people with ASD eventually have strong coherence, which provides better social understanding and compensation of their ToM deficit. However one should note that these are posthoc explanations that attempt to explain exceptions to the original prediction. In other words, the theory may loses in this way its unifying characteristics.

In addition to this controversy, a possible common underlying mechanism of WCC and ToM cognitive deficits is also under debate. Burnette et al (2005) tested this hypothesis and verified a positive correlation performance between verbal WCC measure (two homograph tasks) and ToM tasks (first order and second order), even after verbal IQ had been statistically controlled for; but no correlation between visual-spatial measures of WCC and ToM measure. Pellicano et al (2006) reported that ToM scores were positively related with scores in WCC tasks, but when these results were adjusted for age, verbal ability and non-verbal ability the correlation became nonsignificant. Poor performance in ToM test concurring with fast times on EFT performance and positive relation between performance on false belief tasks and EFT plus Pattern construction, are cited in this same paper. However, they also point out similar neuropsychologic studies that concluded that WCC and ToM are totally unrelated domains of functioning in autism, exposing the lack of scientific agreement in this matter. Overall, these correlation patterns do not yet allow to infer a direction of causality. Furthermore, the identification of non specific factors contributing as common explanatory sources of variance suggests that additional research is necessary in this domain.

b) Executive Dysfunction and WCC

The term executive functions (EF) covers multiple high-order cognitive functions such as: working memory, attention, cognitive flexibility, action planification, inhibition of inappropriate behaviours and selection of appropriate responses. About a decade ago, Russell (1997) was the first defending “autism as an executive disorder” and, in fact, poor performance in executive tasks has been well documented in ASD. Common paradigms used to evaluate planning abilities include the Tower of Hanoi and Tower of London tasks, while the Wiscosin card sorting task is widely use to test perseveration, that is a lack of mental flexibility. Given that ED is an “umbrella” definition, there is a higher probability of executive dysfunction in ASD concurring with other deficits explained by conceptions/theories (Frith and Happé, 1994). Connection to central coherence may be approached in two opposite causal inference directions: better executive functions allow better performance on tasks that demand integration of information to create a “whole picture”; or strong coherence facilitates tasks requiring flexibility and goal-oriented behavior (Pellicano et al, 2006). What this last hypothesis points out is that, in ASD, a preference for local stimuli will create an “overload” of information, making top-down control problematic (Frith, 2003). In a study, conducted by Pellicano et al (2006) where central coherence (CC) and executive function (EF) tasks were performed by children with ASD and a comparison group, results show that a superior performance on central coherence tasks was significantly correlated with better planning, inhibition an set-shifting abilities. But, when age, verbal and non-verbal abilities were controlled, only the performance on the developmental test of visual-motor integration remained related to performance on EF tasks, specially the task involving global processing. Along these lines, spatial abilities are often regarded as one of the strengths in autism and can be justified by both ED and WCC accounts. Edgin & Pennington (2005) examine the relation between spatial functions and those theories, evaluating the performance on spatial, EFs and global/local tasks (two tasks for each aspect). They found that ASD children have stronger performance relative to controls in the CEFT task, in spite of not having a local processing bias. Furthermore their performance patterns were not significantly different in the executive and the perceptual tasks. Overall the authors concluded that their experimental approach provide “little support for either theory” (p.743).

Another crucial aspect within executive functions is attention. Sanders et al (2008), in a review of neuropsychological and imaging studies related to attention, inhibition and cognitive flexibility, found deficits in all these components, to the exception of sustained attention. This data is consistent with unusual attentional features in ASD (fascination with specific objects and difficulty disengaging their gaze from an activity/object, for example). WCC can account for these findings: if we add the fact that ASD children tend to focus on details to the lack of attention control, their interests will be much more restricted as will be their attention to the environment. Frith (2003) metaphorically stated that “an autistic person uses binoculars all the time” (p.180). One might also argue that the inability to disengage from stereotypical behaviour (such as restricting gaze patterns to specific objects) has an executive dysfunction component too.

Executive functions, in contrast with the WCC account , have more objective neural basis, with an explicit correlation to frontal lobe activity as well as fronto-striatal and frontal-parietal pathways (Habib, 2000; Hill and Frith, 2003; Baron-Cohen and Belmonte, 2005; Edgin and Pennington, 2005). However the neurobiological dissection of the cognitive subcomponents of executive function is still at its infancy (Hill, 2004). Ellucidation of these components is critical to establish a solid clinical explanatory model. This lack of specific neurobiological accounts explains why difficulties in these high-order functions are also reported in some other disorders (attention deficit disorder, Tourette’s syndrome, obsessive compulsive disorder, schizophrenia), with ensuing lacking of specificity in which concerns ASD. Another problem of ED theory is that it is not universal, with some studies showing executive functions deficits in only half of their sample of autistic individual (Pellicano et al, 2006). These two last attributes suggest that ED is unlikely to be a core feature of ASD (Baron-Cohen and Belmonte, 2005). Comparability of these studies lies, however, on the assumption that similar measures of EF were taken.

2. Other theories

Alternative neurobiological accounts on ASD are available in the literature, although into some extent they could be interpreted as representing variations or particular aspects of the 3 main theories, and in particular the perceptual aspects of WCC. Also they remain in many of their facets controversial or even unproven. Still, their discussion is relevant to shed light on the neurobiological enigma of autism.

a) Enhanced Perceptual Functioning model

Recognizing the idea of a local bias in autism, Mottron and Burack (2001) have proposed an alternative model to WCC which advocate an enhanced perception as a partial cause of the positive symptoms. In an update of the Enhanced Perceptual Functioning (EPF) model, Mottron et al (2006) pointed out eight basic principles of autistic perception:

1. "The default setting of autistic perception is more locally oriented than that of non-autistics", this implies that there is no deficit in analyzing global aspects or an inexorable use of local strategy, but rather an overall superiority in visual perception.
2. "Increase gradient of neural complexity is inversely related to level of performance in low-level perceptual tasks", meaning a local overconnectivity in what respect to short range connection in regions dedicated to low-level perception, and diminished interregional connectivity (long range connections) across associative areas required for high-level processes. This hypothesis remains unproven but is, nevertheless, testable with current neuroimaging approaches.
3. "Early atypical behaviors have a regulatory function toward perceptual input", mainly lateral glances oriented to moving stimuli, with the goal of decreasing the excessive amounts of visual information that would otherwise had to be processed. This would therefore represent a maladaptive filtering mechanism.
4. "Perceptual primary and associative brain regions are atypically activated during social and non-social tasks", with augmented activation of visuo-perceptual regions (oc-

cipito, occipito-temporal) and less activation of the frontal lobe (high order and in particular executive functions), fusiform face area (face perception) and amygdala (fear and emotion perception). However, this has not yet been proven to be a specific pattern in ASD.

5. “Higher-order processing is optional in autism and mandatory in non-autistics”, in this way there is a greater autonomy of discrimination processes and perception, with a variable influence of top-down control (global precedence, gestalt laws and categorization) in autistic individuals.
6. “Perceptual expertise underlies savant syndrome”, five components being required for this: perceptually recognized elements organized automatically in series; a “brain behavior cycle” with training acquired by perseveration in “sameness”; repeated manipulation of certain objects that lead to “expertise effects”; large exposure to repeated contexts resulting in implicit learning; and, finally, integration of the different elements acquired, leading to generalization. This account is certainly logical, but remains speculative and non inclusive of some identified islet of abilities, at least in some subjects.
7. “Savant syndrome is an autistic model for subtyping PDDs [autistic phenotype unrelated to other diagnosable conditions and/or gross neurological abnormalities]”, because the authors consider that the heterogeneity of the autistic phenotype as a consequence of post-natal overspecialization. Although this notion may be of clinical interest, is little revealing in terms of neurobiological mechanisms.
8. “Enhanced functioning of primary perceptual brain regions may account for autistic perceptual atypicalities”, hence there will be a “specialization axis” toward more posterior regions of the occipital lobe, usually associated to “extraction of unique dimensions”. This argument is in fact a variation of point 4.

Having clarified the concept of EFP and its basic principles, a question follows in our present discussion: in which aspects does EFP detaches from WCC? First, it does not attribute this local bias to a global deficit, but rather to a superiority of low-level perceptual operations. This finer processing on a low-level suggests a development aspect of the theory, according to Mitchell and Ropar (2004). These authors defend that this kind of "expertise" would emerge with increasing age and maturity, not being noticeable at an early point in development. Second, Mottron et al (2006) defend a "mandatory" basis for this bias with differences in brain organization, in contrast with the postulate of a mere "cognitive style" (Happé & Frith, 2006). Nevertheless, both accounts share the idea of a local bias and defend a common mechanism to explain social and non-social features in ASD, according to the authors' view.

On the other hand, not only WCC is deeply related to EFP. This model shares part its conceptual roots with Plaited's (2001) theory of reduced generalization and enhanced discrimination, which in turn was proposed as an alternative to the WCC, although Plaisted recognizes the combination of both perceptual and attentional aspects in WCC account. Simmon et al (2009) pointed out three potential problems in EFP. First, being colour discrimination widely considered a low-level task, it should be enhanced in autism, according to EFP model, rather than reduced as some studies proved (Franklin et al, 2008; Heaton et al, 2008, cited by Simmons et al, 2009). Second, there is a lack of a clear definition of "complex" and "simple" in many visual experimental studies in ASD. Finally, the EFP does not offer an underlying explanation in terms of neuropathology. In fact the the claimed visual hyperacuity ("eagle eye") in autism was actually proven to be an experimental artifact. The most important message is that many of the published papers claiming enhanced perception in ASD have methodological deficiencies that render EFP still a controversial issue (Ashwin et al, 2009; Bach & Dakin, 2009; Crewther & Sutherland, 2009).

b) *Underconnectivity theory*

Underconnectivity accounts are widespread in clinical neuroscience and it is quite surprising that very few papers are available in this respect in autism research. One can mention as an exception the study from Just et al (2004), where brain activation during sentence comprehension was examined using fMRI. They compared high functioning autistic individuals with a control group, not only in terms of cortical areas activated during the task, but also in terms of distribution and synchronization of this activation. Unfortunately, fMRI is not the best method to measure synchronization, due to its low temporal resolution, and the title of the paper is therefore misleading, because more direct neurophysiological techniques are generally used to measure synchrony. The authors were in fact not measuring synchronization but just non-directional correlations. The results are nevertheless interesting. In the autistic group, in comparison to the control group, more activation was found in left superior and middle temporal gyrus (LSTG), commonly named Wernicke's area, and less activation in left inferior frontal gyrus (LIFG), known as Broca's area. The first result might be an explanation to hyperlexicality and unusual strength in processing individual words in autism, as LSTG is related with the meaning of single words. On the other hand, less activation in LIFG, associated with semantic, syntactic a memory processes, would explain the impairment in processing the meaning of complex sentences. In addition to this, they pointed a great difference between the two groups in secondary visual areas, namely occipitoparietal area, which was less activated in the autistic group. The authors found this to be an indication that the autistic group used less mental imagery, which is probably a way to form an integrated representation when processing the meaning of the phrase.

The most important finding reported in this paper was that connectivity between different cortical areas was lower for the autistic group, with a stable pattern of functional connectivity differences among the two groups. In the light of these findings, autistic individuals seem to have enhanced function of particular cortical centers, but few integration of information at higher levels, which depends on synchronization between cortical areas. There are however serious methodological limitations in this study, given that simple correlations were being measured without any directional inference and not synchronization at a fine time scale.

Based on these results, Just et al (2004) presented the Underconnectivity Theory (UT), term used “as a short hand to refer to the underfunctionning of integrative circuitry and emergent cognitive, perceptual and motor abilities in autism” (p.1817). This interesting theory lacks however specific predictions and needs substantial theoretical refinements. Most recent studies do now avoid the use of the term synchrony and report instead functional connectivity analysis. Several imaging studies suggest reduced connectivity when performing working memory (Koshino et al, 2008), executive functioning (Just et al, 2007), mentalizing (Castelli et al, 2002), visuomotor (Villalobos et al, 2005) and face processing (Kleinhans et al, 2008) tasks. A study of functional connectivity[1] during resting-state (Cherkassy et al, 2006), expanded the pervasiveness of underconnectivity in autism, being this lack of coordination present not only in complex tasks, but also in the “default mode”. Another interesting finding was a negative relationship between frontal-parietal connectivity and Autism Diagnostic Observation Schedule (ADOS) scores, so that severity of autism was associated with lower connectivity (Just et al, 2007).

Anatomically, abnormalities in the connectivity between the two hemispheres, particularly in what respects to fronto-parietal (Just et al, 2007) and anterior-posterior medial cortex (Cherkassy et al, 2006) connectivities, were reported. In the future, besides fMRI, other technologies might be applied in UT research such as electrophysiology, DTI and histology, contributing for future refinement of this account (Koshino et al, 2008).

In spite of growing evidence accounting for UT in autism, some studies are not consistent

[1] Functional connectivity is defined as a correlation between the average time courses of all voxels in each member of a pair of regions of interest (Cherkassy et al, 2006; Koshino et al, 2008). This low scope methodology, in fact has now been superseded by the more accurate methods of effective connectivity, dynamical causal modeling and Granger Causality.

with a generalized underconnectivity (Villalobos et al, 2005) or even show an increase of functional connectivity between thalami and cortex (Mizuno et al, 2006).

The final question is what are the boundaries between UT and WCC? As Just et al (2004) had clarified, UT is inspired on WCC, searching for a biological underlying mechanism that lacks on Frith's account. In the same paper, two important differences were adduced by the authors: first, UT emphasizes the role of the dialogue between cortical areas, contrasting to WCC which implies a central coherence processor; second, contrary to WCC which does not divide the cortical system into its components, UT is about cortical centers as components and underconnectivity fosters the development of a less integrated, more autonomous set of such processing centres.

However, even before the emergence of UT (Just et al, 2004), Hill & Frith (2003) while admitting the lack of underlying neuro-physiological processes for WCC, defended that it "alludes to poor connectivity throughout the brain" (p.284). Indeed, we found soft boundaries between UT and WCC so that, when debating electrophysiological and imaging studies further in this paper, some of the presented results possibly account for both. The question can then be raised whether UT could just be seen as neurobiological account of the WCC, which is more centered on the cognitive process itself.

c) *Empathizing-Systematizing (E-S)*

In ASD research some epidemiological (ratio male vs. female of 4:1 in autism and as high as 15:1 in Asperger Syndrome, see Frith, 2003), biological (Knickmeyer et al. 2005) and behavioural evidence (see Baron-Cohen, 2002) suggest ASD as an extreme of male brain characteristics. Exploring this idea and the fact that male individuals have better systematizing than emphatizing qualities, Baron-Cohen (2002) proposed a new account for ASD structured by these two dimensions. Emphatizing, which would be impaired in ASD, comprises not only the concept of mentalizing, i.e. attribution of mental states to others, but also the capacity to give an appropriate emotional response to that mental or affective state. Hence, empathy constitutes a pillar of social function. On the other hand, systematizing, enhanced in ASD, is almost dispensable for predicting changes in a person's behavior, but is essential to deduce the inanimated universe behavior, guided by strict rules. Systematizing implies observing correlations between different local features, which require focusing on a detail of a system and observing how it varies. This is where Baron-Cohen's theory overlaps WCC, because the first step of systematize is initial attention to exact detail and attention to local detail is the foundation of WCC (Frith, 2003; Baron-Cohen and Belmonte, 2005; Happé and Frith, 2006). However, local detail and local rules are not enough to make up a system. Systemic rules and the establishment of relations between constituent elements are also needed in this process, suggesting that "systematizing theory predicts, but is not predicted by weak central coherence" (p.253) (Baron-Cohen, 2002). E-S predicts that ASD individuals are able to learn the functioning of any complex system, as long as it is rule-based, in opposite to WCC which is oblivious to the possibility of understanding how a system works (Baron-Cohen and Belmonte, 2005). According to the same authors, one might approach E-S and WCC as complementary theories, with a cause-effect relationship. The question is whether WCC is an early manifestation of enhanced systematizing, or systematizing is a consequence of attention to detail.

Despite the attempt of some comprehensive studies to established links between cognitive deficits and brain function[2], a common defect of WCC and E-S stills being the lack of an identified neurobiological basis, as stated by Sanders et al. (2008).

[2] See Baron-Cohen (2005) for data proving high activation at low levels of processing and low activation at high levels of processing.

THE VISUAL PIECE TO COHERENCE

An extraordinary facility with jigsaw puzzles is common in autism. However, the way children with autism prefer to construct a puzzle may be quite different from the way a normal child does it.

(p.151; Frith, 2003)

The metaphorical concept of Weak Central Coherence Theory is precisely doing a puzzle just by linking piece to piece in small groups until eventually complete the task, but without looking, as a cue, to the final picture usually presented in the puzzle box. That is, in the light of this account, autistic individuals have a detailed-focus processing, with a failure to extract global form. The account had been refined and, now, generally considered as a processing bias for local information: a "cognitive style" which can be modulated to some degree, rather than a rigid inability to achieve overall perceptual Gestalt. Consequently, WCC predicts either superiority or inferiority of performance on perceptual tasks depending on whether these demand local or global processing, respectively (Dakin & Frith, 2005).

Among various perceptual modalities (named in this paper's introduction), enhanced visual-spatial ability is the most distinctive, with excellent performance in BD and EFT often contrasting with severely impaired language. Moreover, the majority of perception studies in autism are in the visual domain and there is significant anatomic and physiologic knowledge of vision brain pathways. These are some of the aspects that made visual-spatial ability an appealing theme of debate in autism research and the main topic of this paper.

A wide range of studies in ASD visual spatial ability have been published. In this article, we aim to review behavioural, neurophysiological and imaging studies related to visual perception and discuss how they link to the Weak Central Coherence Account. However, we will first contextualize those studies by providing some background on normal visual processing.

1. VISUAL PROCESSING

Once the visual input achieves the retina, electromagnetic radiation is converted in neural signals by the 125 millions of photoreceptors (rodes and cones) lying in its outer segments (Bear et al, 2007). These cells send those neural signals to bipolar cells which, in turn, communicate with ganglion cells in the innermost layer of the retina. Ganglion cells are the only source of output from the retina and it is here, at the early stages of visual processing, that the dichotomy local/global begins (see Figure 1). We must consider to this discussion two main types of ganglion cells with significant morphological differences (Polyak, 1941): midget ganglion cells, characterized by dense compact dendritic arborization, and parasol ganglion cells, with few dendrites widely distributed. The first subtype primarily connects with the four dorsal/superficial layers (3-6) of lateral geniculate nucleus (LGN), forming the parvocellular stream which is optimally activated by stimuli with high contrast and high spatial frequency. That is, smaller and more detailed aspects of the scene are conveyed in this pathway. On the other hand, parasol ganglion cells project to larger cells in the two deeper (1-2) layers of LGN to compose the magnocellular stream specialized in the perception of motion and *low* contrast stimuli. In this way, low spatial frequency signals, processed in this pathway, contain information about coarse/global properties and arrive at the cortex more rapidly (Milne et al, 2002). Both magnocellular and parvocellular streams have a common cortical target: the primary visual cortex (V1, striate cortex or area 17 from Brodmann's classification), despite some synapses being made in different layers.

Neurons in V1 are primarily responsive for locally oriented image structure within a confined area of visual space known as receptor field (RF). Depending on their size, RFs confer sensitivity to structures with different spatial frequencies: small RFs to high frequencies and large RFs to low frequencies. However, it has been proven that V1 neurons receive inputs from other neurons in the neighbourhood, those being of facilitation or inhibition, and feed-back projections from higher visual areas. Those “long-range” horizontal connections would be responsible for giving a context to the visual stimulus. V1 also sends projections to extra-striate cortical areas in a hierarchical fashion. All these cortical connections contribute to a relatively spatially extensive global integration of V1 inputs (Dakin & Frith, 2005).

How is this hierarchy organized? As stated before, V1 receives all visual input and the processing of color, motion and shape begins here. Subsequent neurons will have larger RFs, allowing for more spatially extensive global integrations. Thus, visual process continues through two different circuits (Habib, 2000): one is implied in processing motion and projects up into the MT/V5 complex, the other responds to shape and color (static aspects) and includes V2, V4, VP (ventral V3). The final target in the first case is parietal lobe[3] and this constitutes the dorsal visual pathway, also known as the “where” ”vision for action” (“how”) stream, as being responsible for localization of visual moving stimulus and consequent reaching towards objects. The second circuit, named ventral visual pathway, ends in the inferotemporal area and represents the “what” stream, because it is involved in recognition of objects (including fine analysis in terms of texture, colour, fine pattern and form) and spatial relationships between them. It is believed that dorsal stream receives preferential input from magnocellular layers of LGN, while the ventral stream receives input from both magno and parvocellular layers (Milne et al, 2002; Tsermentseli et al, 2008).

[3] Connections with frontal lobe were also recently proved, suggesting that dorsal stream was also implicated in visuomotor coordination and giving rise to the additional denomination of “how” stream (Villalobos et al, 2005).

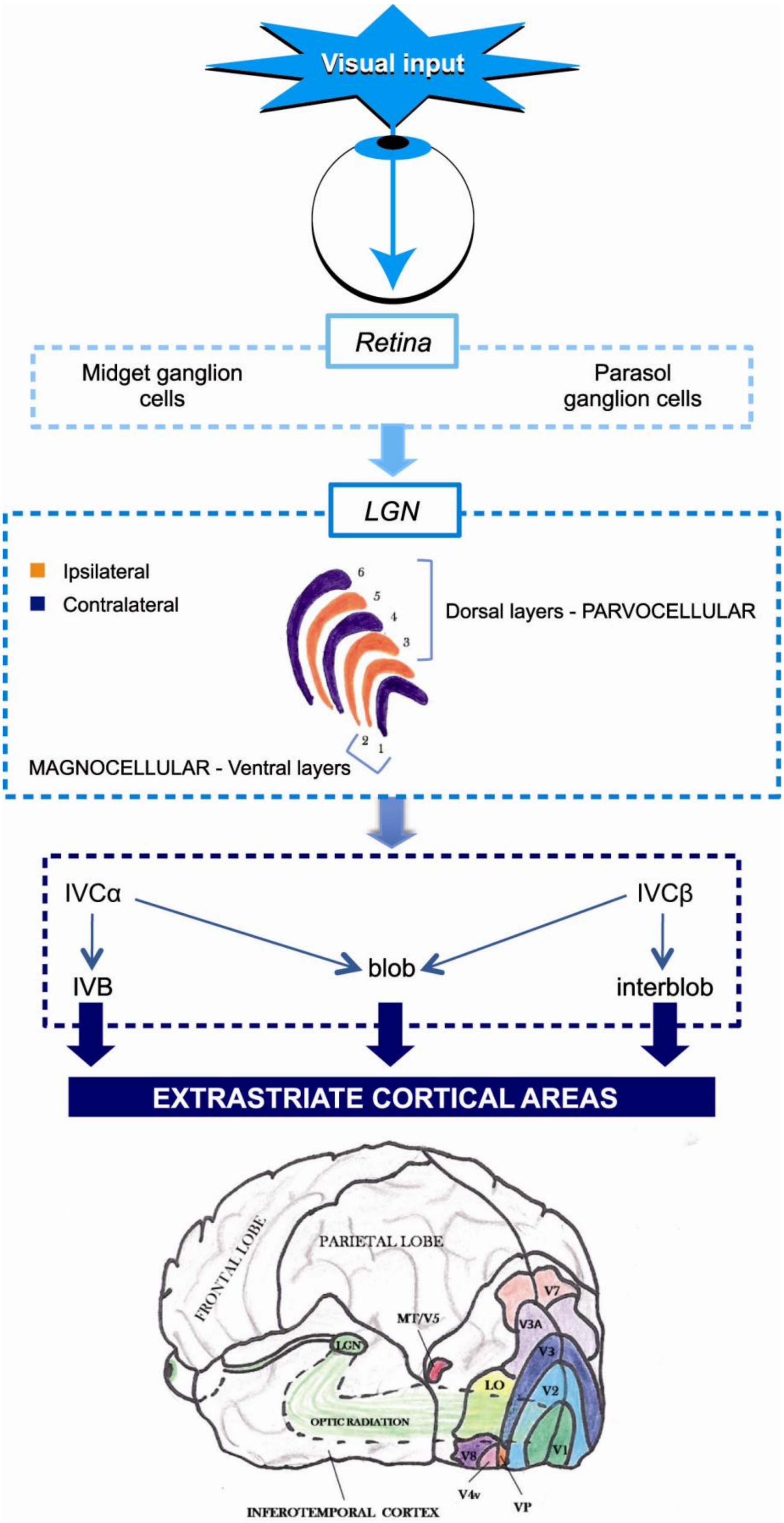

Figure 1- Fundamental organization of retinocortical visual pathways.

To summarize, in human visual system, neurons become more selective, processing increasingly complex features. First, two streams process separately coarse-scale motion and fine-scale form information, both achieving the primary visual cortex. In sum, two independent pathways process location and identity of objects. (Dakin & Frith, 2005)

2. Psychophysical, Behavioural and Clinical Studies

In this section, we review studies that have used local/gobal tasks in individuals with ASD, with the goal of exploring WCC in the visual domain.

a) Block Design Test

In the Wechsler Intelligence Scales (WISC for children, WAIS for adults), a combination of 10 subtests applied worldwide for IQ evaluation, autistic individuals usually present a remarkable pattern with two opposite poles of performance. The worst performance lies on the Comprehension subtest, considering it demands good communication skills and social context or shared cultural knowledge. In contrast, autistic individuals performed as good as or better than normal children in the Block Design subtest (Frith, 2003), with BD test peak being present in 47% of autistic individuals (n =92) contrasting to 2% in typical individuals (n =112) in a study by Caron et al (2006). In this way, it is considered a useful cognitive measure to discriminate children with autistic behavior from those without it (Best et al, 2007). BD test consists in arranging four or nine blocks (each one with two white sides, two black sides and two white and black sides) to make a given global pattern. To succeed in the task, individuals must breakdown the global picture into details. "Good" performance in this task, as characterized by low reaction times, is considered an index of WCC (Baron-Cohen & Belmonte, 2005; Burnette et al, 2005; Happé & Frith, 2006; Happé & Booth, 2006). One should point out that it may seem counterintuive to equate good ability to decompose the blocks into components and then rearrange them in a global pattern with weak central coherence. To study this principle, Shah and Frith (1993) tested variations of the block design task: segmented or unsegmented, rotated or unrotated, and containing or not obliques. Autistic individuals performed better than controls in the unsegmented condition and show less advantage from using pre-segmented designs, which clearly suggest that autistic subjects have a greater ability to segment a gestalt. In addition to this, the other conditions (rotation and obliques) affected all groups equally, so that the excellent performance in BD would not be due to superior general spatial skill. This experimental task from Shah and Frith (1993) has been reproduced by several researchers, as reviewed by Simmons et al (2009). In this revision work, the authors pointed the BD test as a defective measure of visual perception, as it involves several stages (segment the image, choose the blocks and construct them) and a deficit in any of them could lead to poor overall performance. Caron et al (2006) explored the cognitive and cerebral mechanisms possibly underlying the Block Design peak in autism. They compared the performance of 8 autistics with a BD peak (HFA-P), 8 autistics without a BD peak (HFA-NP), 10 typically developing participants (TD) and 8 gifted individuals with a BD peak (TD-P) in a battery of five modified-block design experiments, administered in the same order to all participants. The first task varied in three grades of perceptual cohesiveness (PC) (pictures with higher cohesiveness required more segmentation skills) and presentation (segmented/unsegmented) (see Figure 2).The second task consisted of matching an unsegmented figure (chosen from 4 given options) to a corresponding segmented target figure, and pretended to evaluate holistic processing. Experiment 3 tested long-term visual memory for block-design figures and experiment 4 investigated featural and conjunctive visual search. At last, the fifth task assessed discrimination threshold and perceptual encoding speed for meaningless visual patterns. Despite the size of the sample being not the ideal, some crucial conclusions were presented: (1) both HFA groups showed less influence of increasing perceptual cohesiveness; (2) however, autistic individuals preserve their ability to integrate features into coherent wholes; (3) HFA-P clearly had superior performances that IQ-matched participants; (4) no differences in performance or profile were found between HFA-P and the gifted BDT-matched. These last conditions may offer an explanation for the lack of success in finding differences in BD test performance in some studies (e.g. Bölte et al, 2007) independently of autistic individuals and controls being precisely matched for measures of IQ. We may also summarize the results of this study by saying that the local bias in autistic individuals is not necessarily predictable of a superior performance in BD test. Accordingly, Caron et al. (2006) suggested that the default local bias presented by individuals with ASD is bypassed when a global perceptual perspective is required for correct performance in certain tasks. These authors have even suggested that autistic group appears to be more cognitively versatile than the TD group: they may use a locally oriented or a globally oriented strategy, depending on task constraints. In fact, is the local processing bias in performing BD test that seems both sensitive and specific of autism (Bölte et al, 2008).

Subtests of Wechsler Intelligence and Differential Abilities Scale Scales that are also used to assess WCC are the Object Assembly and Pattern Construction tests, respectively (Burnette et al, 2005), but usually autistic individuals do not have deficits in this performance (Happé, 1994 cited by Jolliffe and Baron-Cohen, 2001). A possible explanation is that autistic individuals may construct the object in a “bottom-up” way, matching lines and edges of small elements in a serial way (Jolliffe and Baron-Cohen, 2001; Happé and Booth, 2008). However, for some authors (Edgin and Pennington, 2005) this cannot be explained by enhanced local perceptual bias, because it requires the construction of whole objects out of pieces sometimes destitute of local elements.

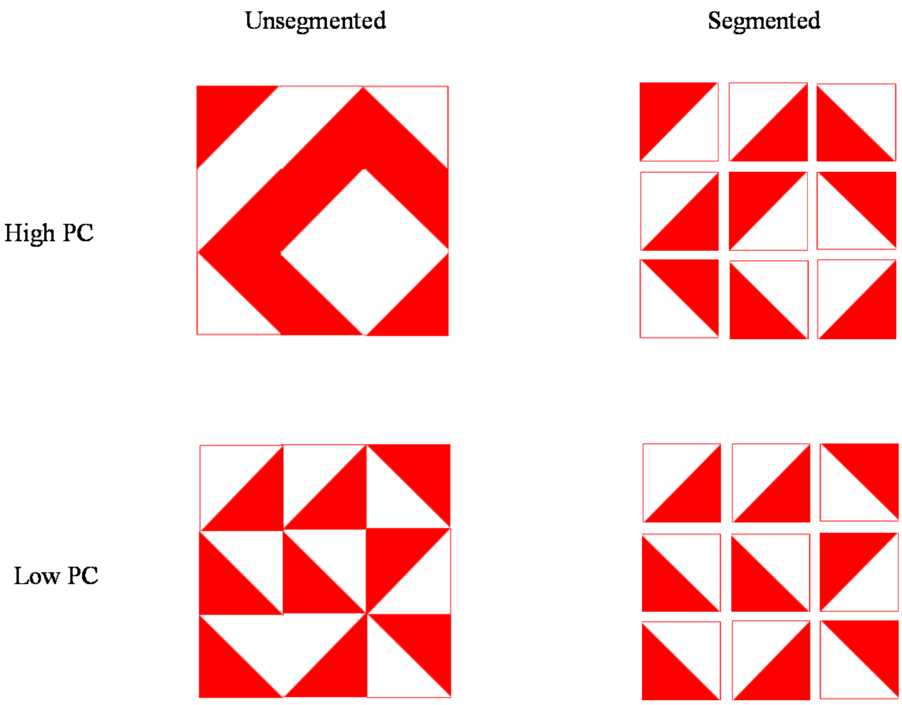

Figure 2 – Examples of Block Design stimulus types, adapted from Caron et al (2006).

b) Embedded Figures Test

Besides BD, other classic example of superior performance task in ASD, when capturing the global picture is disadvantageous, is the Embedded Figures Test (EFT) based on two-dimensional visual search (in opposite to the three-dimensional construction of BD). EFT requires the subject to perceive a simple geometric figure hidden in a more complex and camouflaging picture. Thus, stronger influence of context in visual perception and social interaction corresponds to worst performance on the task, being a clear advantage to have "weak coherence" or dominance of local segmentation. On the other hand, quick and successful search of the embedded figure might be due to great ability to focus on the salient part, ie superior local processing (Bölte et al, 2007; Happé & Frith, 2008). Notice that major differences between the autistic group and controls performance in EFT refer to reaction time, being both groups of participants frequently close to ceiling in the task in terms of accuracy (Jollife & Baron-Cohen, 1997; Edgin and Pennington, 2005; Bölte et al, 2007).

However, this explanation of good performance in EFT based on WCC account is not universally accepted. In a study with 24 children with HAD and Asperger's Syndrome, Edgin and Pennington (2005) tested the comparative performance (autistic group vs. control) in EFT and two measures of global and local processing: (1) Banks and Prinzmetal task, which requires the child to find T's or F's deeply embedded or not in distractors (forms halfway between a T or F), and a first condition where elements are grouped to form an X, being the global figure a distracter itself (2) Huttenlocher task, in which participants have to remember the location of a point in a circle. In this test typically developing children present a bias towards the centre of the quadrant where the circles are. ASD performance in EFT was better at younger ages, but was similar to control group in older ages. In both local/global processing tasks, no differences in perceptual bias were found between ASD and control groups. From these results, the authors concluded that the performance in EFT could not be explained by differences in local and global processing in the ASD group. In spite of some studies disconfirming superior performance on EFT and BD (Burnette et al, 2005), those are still the two pillar tasks providing supporting evidence in favour of WCC with considerable consensus among researchers.

c) *Visual Illusions*

Weak central coherence has also been tested in low-level visual tasks, such as visual illusions, for the first time by Happé (1996). According to this account, if autistic individuals are less influenced by the context, than we can predict that they would succumb less to the effects of visual illusions, such as the Ebbinghaus Illusion or Titcheners' circles (Figure 3), where the surrounding circles (distractors) modify the perception of the inner circle (Frith, 2003). Other examples of visual illusions frequently used in autistic research are the Müller-Lyer (Figure 4) and Ponzo (Figure 5) illusions. Another aspect related to the fact that visual illusions involve simple perceptual judgment is that this leads to the expectation that performance on the visual illusions should, in principle, be uninfluenced by IQ (Best et al, 2007). However, some authors defend that since susceptibility to visual illusion is considered a fundamental characteristic of perception, than not succumbing to those would be a characteristic of a person with noticeable severe abnormalities in perception (Mitchell & Ropar, 2004). This may not be true if we considerer that low level of these phenomena, as variants in perceptual organization, akin to the concept of a different visual processing style, whereby global context is not a strong factor in very early stages of perception (such as magnocellular pathway that we will discuss further), rather than a severe, general and obvious deficit in visual processing.

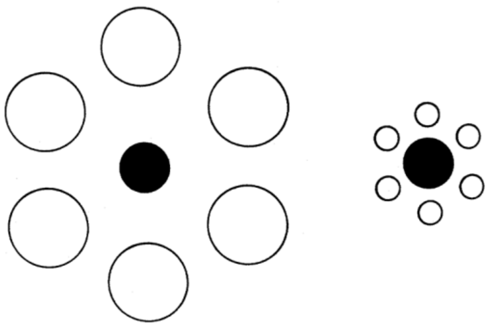

Figure 3 – The Ebbinghaus Illusion

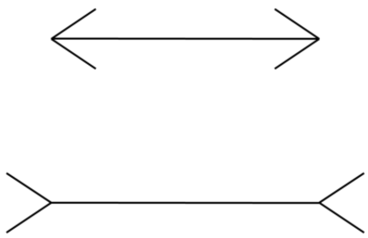

Figure 4- Müller-Lyer Illusion

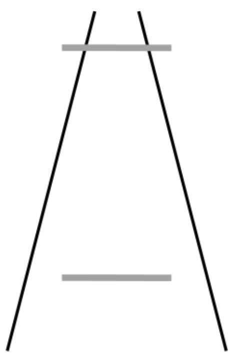

Figure 5 – Ponzo Illusion

The main incongruity in this subject raises from some studies that, not only failed to demonstrate lower susceptibility to visual illusions in autism, but also found no relation between visual illusions and other measures of WCC, such as BD, suggesting that they do not have a common cognitive origin (Mitchell & Ropar, 2004; Best et al, 2007). In the interpretation of those contradictory studies we must take into account some methodological differences that my have significant impact in the results, such as the type of illusions, how they are presented to participants and how the instructions are given, as well as the response method (verbal vs. manual). Other aspect that is relevant to consider is whether low susceptibility to visual illusions are specific of autism or not. A study (Bölte et al, 2007) involving 15 participants with HFA, 15 with depression, 15 with schizophrenia and 15 typically developed (control), concluded that not only the individuals with HFA succumbed less to visual illusions, but also the groups with depression and schizophrenia. In line with these results, the authors suggested that, in autism, early perceptual abnormalities might be a phenomenon not specific to autism, but shared with other mental disorders, which have demonstrated overlaps regarding cognitive malfunction. Interestingly such overlaps occur mostly in the executive function domain.

Remarkably, the hypothesis of autism as continuum in general population has also been tested trough visual illusions (Best et al, 2007; Walter et al, 2009), being identified a significant correlation between the autistic trait of systemizing and susceptibility to a subset of the tested illusions. However, one should take into account the observations of Best el al (2007), that performance in the visual illusions, did not contribute to prediction of behavioural traits.

d) Navon Figures Test

Navon (1977) tested the principle of global precedence, which he symbolically described as seeing “the forest before the trees”, based on the presentation of a large letter built up from small letters and on the tendency of normal observers to report the global shape (letter) instead of the small items (letters) that compose it (see Figure 6). From a set of 4 experiments, he concluded that global processing is normally done prior to local processing and that, whereas local level has no effect in global recognition, global cues have usually inhibitory impact in the response to the local level. Since then, Navon task is largely used in psychological tests, particularly in autism to test a drive for local processing. Navon test stimuli are also known as hierarchical letter, enclosing the principle that this detection tasks require switching attention between levels or attentional scale (Iarocci et al, 2006). Consequently, some authors defended that autistic individuals have a deficit in "hierarchical perceptual organization", presenting a lack of global precedence over the local level, but maintaining the ability to global and local processing, distinctively from the WCC account (Mitchell & Ropar, 2004). The results of many experiments with hierarchical stimulus in autistic population are not concordant with this view and the controversy is ongoing. Some studies interpret results on the basis of presence of both local advantage and local interference with impaired global advantage and global interference (Plaisted et al, 1999). However, the extent into which the WCC account is supported by specific local advantage and local interference effects (Plaisted et al, 1999; Lopéz et al, 2004, Mitchell & Ropar, 2004; Simmons et al, 2009) needs a more thorough experimental dissection of speed vs cognitive bias vs perceptual performance factors.

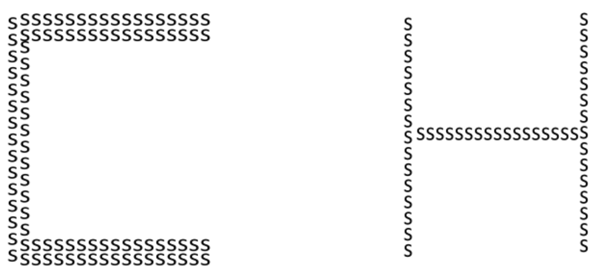

Figure 6 – Examples of hierarchical letter stimulus

According to the need of separating bias from performance issues, Iarocci et al (2006) designed an experiment with slightly different hierarchical stimuli: global targets were diamonds or squares made of circles, local targets were circles made of diamonds or squares, and circles made of circles were presented as distractors. In this experiment there were three conditions which varied in the likelihood of appearance of the target at the local or global levels : (1) a global bias condition (global target presented 70% of the time and local level 30%), (2) local bias condition (the inverse), and (3) neutral condition (the target was equally likely at the local and global levels). The research also involved another experiment consisting in a visual search task. The main goal was to create a bias so that global or local processing was favored and find the susceptibility to such bias in autistic and control populations. Their results demonstrated that, both groups responded more rapidly to global targets. It is quite surprising that children with autism, like all children in this experiment, responded to global targets more rapidly than to local targets, and although this effect of Target Type was smaller in this group it was significant. In general they were more sensitive to biasing manipulations, so they adapt better to the implicit demands of the task. This differently organized attentional distribution would lead to atypical perception of objects and events. What are the connections with WCC account at this point? This unusual pattern of high-order coordination of attention helps setting priorities “to attend to one level of the structure over another” (p.127, Iarocci et al, 2006). In other words, autistic individuals would have a “piecemeal” or “data driven” style. In any case it seems clear that this flexibility in bias manipulation is not explicitly predicted by the WCC account.

We conclude this section with two commentaries related to experimental issues. A first note about Navon figures pointed out by Navon himself (2003): experimenters that investigate the disposition of global/local perception should take into consideration the particular shape of letters as an additional influence in local-global effects. This has justified the use of other types of shapes (for example O and Cs, rather than S or Hs). Secondly, one needs to carefully consider the meaning of "global grouping". Dakin and Frith (2005), in a review article, established the following operational definitions: (1) a local structure is processed by single neurons in V1; (2) a global structure requires coordination of several neurons' activity. Based on this criterions, the authors defend that Navon figures and other tasks involving "gestalt grouping" of simple dot patterns (eg, Jarrold & Russel, 1997; Iarocci et al, 2006), would be processed only by neurons with large receptive fields in high order visual areas. Consequently, the operation of neurons with large receptive fields, sensitive to low spatial frequencies, would be sufficient for detection of global structure without recourse to dedicated global grouping mechanisms that link multiple receptive fields across space. This might put lead to some interpretational problems in studies involving those tasks.

The inverse mechanism is observed when using high pass filtering techniques (low spatial frequencies removal), with slower response times to global level and enhancement of local level, supporting the idea of magnocellular impairment underlying local processing bias in autism (Milne et al, 2002). We will return to this concept further in the present article.

e) Achieving the "whole": Impossible Figures, Fragmented Figures and Drawings

Paradoxical figures and fragmented figures tasks have a peculiar purpose in ASD and WCC research as they were designed to analyze global integration by itself, if possible without a local processing *bias*. In other words, the aim of those tasks is to achieve the "whole picture". Paradoxical figures are termed as such because they are locally congruent, but geometrically impossible when globally perceived. For this reason the judgment of Impossible Figures (as they are also known) should be problematic for autistic individuals according to WCC theory, due to defective integration of details. This hypothesis was tested by comparing autistic and controls' drawing times of possible and impossible figures. Unlike normal controls, who took significantly longer time to draw impossible figures, autistic individuals did not show this effect (Mottron et al, 1999; Sheppard et al, 2009).

Jollife & Baron-Cohen (2001) came up with one of the few studies with Fragmented Figures, singularly correlating WCC with visual conceptual level (high-level or top-down process), involving three groups of participants: autism, Asperger and control ones. To carry out this experiment, they modified the Hooper Visual Organization Test, originally applied to organic brain conditions to evaluate the ability to integrate different visual elements, so that two conditions were created. In the first condition multiple fragments of a picture were presented and the participant had to integrate those elements for successfully identify the object. The second condition tested the ability to recognize an object from a single part. For both conditions two performance measures were took into account: response time and accuracy. The results showed different performance only in the first condition, in which autism group was the less efficient, followed by the Asperger group, with the control group performing significantly better than both other groups. This was in agreement with predictions made by WCC account. However, the authors pointed out one incongruity with this theory: despite the increase in response times as the number of elements increased, the same tendency was not observed for accuracy. Indeed, if autistic individuals had weaker coherence, than a greater number of elements to integrate should have been reflected in worst performance.

Nevertheless, the visual conceptual gestalt level can be tested with other tasks besides fragmented pictures. In an interesting experiment (Nakahachi et al, 2008), involving an novel visual task, a group of subjects with ASD (3 with autism and 7 with Asperger's Syndrome) and a control group were asked to find differences between an original picture and two similar images slightly modified (distractors), in a set of 10 different original pictures illustrating life events. The first distractor (D1) contained a change related to the main theme, in the second distractor (D2) the difference was not related to the context. The original picture had to be memorized in 10 s and after that D1, D2 and a replica of the original picture were presented one by one in a random order. Only in D1, autistic performance was significantly worse comparing to control group, which means that they do not use contextual information to memorize a pattern. This are encouraging results for the WCC account, even so it will be important to reproduce the study with a larger sample. However, one needs to take into account that effective use of contextual information might also be invoked within the framework of striatal/executive dysfunction (van Asselen et al., 2009 a, b).

Moreover, in ASD is quite typical (but not pervasive or constant!) to find two types of alternative drawings: one, with enhanced local processing, although achieving a final picture correctly configured; in the other, there is a total violation of configuration without evidence of local focus (Happé and Booth, 2008). In addition to this, special ability for drawing is considered one of the savant talents (Frith, 2003), because it is possible that, in terms of artistic performance, attention to details turns up to be an advantage to accomplish a brilliant "whole picture". However, there is a substantial conceptual problem: drawing in a piecemeal like manner leads very often to strong errors in proportion and perspective, which is a problem well-known to art students and professionals. In other words, autistic savant painters pose a strong challenge to the WCC account.

f) Visual Motion

We have already mentioned the role of magnocellular pathway in autism physiopathology when discussing perception of Navon figures. A way of testing magnocellular processing is by using motion coherence stimulus, which comprehends a large number of dots, moving randomly, of which a small proportion moves coherently in a certain direction. This confers a transient perception of motion and the minimum number of dots moving coherently needed to the observer discriminates direction defines the threshold for the task (Dakin and Frith, 2005; Simmons et al, 2009). A high motion coherent threshold indicates either impairment to the afferent magnocellular pathway or to the areas directly processing motion coherence (MT/V5, posterior parietal cortex) (Milne et al, 2002, Castelo-Branco et al, 2002). It is important to notice that there is some scientific evidence that neural responses (V5) to motion coherence are linear, allowing for a roughly linear analysis of participants responses in motion coherence studies (Tsermentseli et al, 2007). These studies are usually run as two alternative forced choice tasks (2AFC).

Milne et al (2002) performed an experiment using a Random Dot Kinematogram paradigm, in which they matched individually 25 autistic children and 22 control participants according to chronological age and non-verbal IQ, rectifying a possible methodological failure of Spencer et al (2000). Both studies reported increased motion coherence thresholds in autism. Spencer et al (2000) claimed a specific impairment in dorsal stream function. Milne et al (2002) discussed these results in the light of WCC account, suggesting that low activity levels in low spatial frequency channels, which are associated to magnocellular pathways, might be the underlying cause of focus on local aspects as opposed to the global aspects. Note, however, that Castelo-Branco et al. (2007, 2009), have shown, both in neurodevelopmental, stroke and neurodegenerative disease models, that motion coherence deficits are not necessarily explained by magnocellular deficits . This is to be expected from the fact that the magnocellular system is just the afferent pathway to the motion coherence system, and that this can therefore be lesioned independently.

Furthermore, knowing that magnocellular processing occurs in parallel with parvocellular signalling, in the early stages of visual processing, it can be questioned whether the performance differences are due to imbalance of activity between parvocellular and magnocellular systems. On the other hand, in Milne et al.'s (2001) study the mean threshold for the autism group was 25,05%, but with a range of 6-64%, which means that not every autistic participants had high motion thresholds. These results suggest that the magnocellular/motion coherence deficit might not be a necessary condition in autism. Finally, Milne et al (2002) suggested that, to prove causal relation of magnocellular/dorsal stream deficit with weak central coherence account, a study should be conducted correlating motion coherence thresholds and performance on classical central coherence tasks.

Pellicano et al (2005), following the suggestion, administered the Children's Embedded Figures Test (CEFT), a global dot motion task (GDM) and a flicker contrast sensitivity task (FCS) to twenty children with ASD and twenty typically developing children. GDM pretended to assess higher-level dorsal stream function, while FCS assesses lower-level visual processing. Children with ASD showed significantly higher motion thresholds (22,4%) than typically developing children (11,10%) and performed more rapidly in CEFT. However, there were no significant differences between ASD and control groups in sensitivity to flicker. Since performance in GDM and CEFT were inversely correlated, we can deduce that a deficit in high-level areas of the dorsal visual pathway contribute to lower performance when processing static or dynamic stimulus as Gestalts, as predicted by WCC account. But, what does the lack of significant differences in FCS mean? In fact this result is consistent with the above reported findings of Castelo-Branco et al. (2007, 2009), showing that these types of deficits are not originated in the afferent pathways.

In line with the proposed explanation are the results of Berton et al (2003), who applied a motion discrimination paradigm to investigate whether there is dissociation in sensitivity between first-order (luminance-defined) and second-order motion stimulus (texture-defined). Thus, autistic individuals showed less sensitivity to second-order motion, a more "complex" motion class processed further along the dorsal visual pathway; but, typical first-order motion discrimination, processed in the primary visual cortex. Pellicano et al (2005) adopted in their experiment FCS as a first-order motion[4] and GDM as second-order motion. In conclusion, both articles defend no early impairment of the afferent pathway to the dorsal pathway in autism, but rather a more specific motion integration deficit.

However, some studies do not corroborate the results from Pellicano et al (2005), with the one by Del Viva et al (2006) being in stark contradiction to the first. Detection and coherent thresholds for Gabor patches optic and flow motion stimuli, respectively, were measured and results showed no differences between performance of autistic and normal participants. Both studies were extensively reviewed and compared by Simmons et al (2009) in terms of sample selection, stimulus used and other methodological aspects, with the authors concluding that the study from Del Viva et al (2006) was the more methodologically correct of the two.

Another study finding no evidence of impaired global motion perception in ASD was the one by Vandenbroucke et al (2008). This time, dissociation of low vs. higher order visual stimulus was tested using a plaid stimulus: two superimposed squared-wave gratings moving in different directions. This is perceived in two forms corresponding to two stages in visual pathway: (1) as two gratings (component motion), one transparent surface above the other, at an early stage; (2) as a single pattern (coherent motion) with an intermediate direction, established by a higher-order mechanism. In the context of this hierarchical organization to surface segregation, Castelo-Branco et al (2000) proved that neurons located in early visual areas (A18 and PMLS - postero-medial bank of the lateral suprasylvian sulcus) of the cat cortex are mostly component-specific, being sensitive to individual grating, and do not discriminate between component and pattern (coherent) motion. However, they do synchronize differently according to transparency and direction, being the differential synchronization patterns that trigger the joint processing at further levels. According to this, Vandenbroucke et al (2008)

[4] In a strict sense this is not sensitivity to motion but to temporal modulation instead.

showed that autistic subjects have impairment in object boundary detection/surface segregation, possibly due to imbalanced feedforward vs. feedback processing.

Other type of motion that is also being used in testing integration of dynamical information is the biological motion: representations of human or animal actions using point-light displays (PLDs). As reviewed by Dakin and Frith (2005) and Simmons et al (2009), the interpretation of data on biological motion has so far been complicated by concurrent low-level difficulty with motion processing "feeding through and complicating the interpretation of biological motion stimuli"(p.2715, Simmons et al, 2009). It is also clear that high level cognitive processing of such stimuli will be different, because of the ease with which typical observers can attribute emotions and feelings to these curiously sparse stimuli. However, in which concerns a specific visual deficit, there is no agreement if biological motion in autism is impaired (Klin et al, 2009) or not (Hubert et al, 2007). Hubert et al (2007) interpreted good ASD performance in describing PLDs as an argument against the WCC account, defending that if autistic children are able to perceive those meaningful representations of people or objects, it implies that they have integrated PLDs into a whole. One striking study (Klin et al, 2009), performed in 76 autistic children with a mean chronological age of 2.05 years, showed instead that this group failed to recognize PLDs of biological motion, but was highly sensitive to physical contingencies (non social stimulus). This lack of preference to social stimulus in such an early stage of life certainly would have several implications in neural and behavioral specializations. As a cautionary note, it must be said that the preference bias introduced by non social stimuli has in future studies to be distinguished from real impairment.

The contradictory reports on this recently exploding area of research in autism lead us to some considerations related to interpretation problems or methodological differences possibly biasing the results. First, it has been suggested that eye movements may influence perception of a moving pattern and it also known that a autistic individuals present a higher rate of eye movements, so this should be controlled in visual experiments (Vandenbroucke et al, 2008). Other aspect that might contribute to poor performance visual motion tasks are the attentional deficits often present in autistic populations, such as impairment in shifting attention and greater susceptibility to distracters (Brenner et al, 2006). Besides that, it has been suggested higher attentional demands in second-order motion tasks (as reviewed by Dakin and Frith, 2005). Tsermentseli et al (2008) emphasizes that the bulk of visual perception experiments in autism do not differentiate participants within autism spectrum disorder, which might be an important methodological lapse, since their own study found motion detection to be intact in Asperger Syndrome and impaired in HFA. In this same paper the authors pointed out as a methodological failure, not measuring the language ability of participants, as it has been reported that performance in high-noise tasks is linked with language and literacy skills. Tasks used as static control for motion coherence stimuli may be problematic too, as denoted by Dakin and Frith (2005). They considered, as an example, the control task used by Spencer et al (2000) totally limited by global pooling and suggested as control task the Glass pattern, as performed further by Tsermentseli et al (2008). Finally, and as stated above, some care is recommended when equating magnocellular and motion coherence deficits and assuming correlations for tasks that have a neural substrate in different levels of visual pathway. Indeed, it was found that magnocellular impairment is not directly related to higher levels of motion perception (Castelo-Branco et al, 2006, 2007, 2009).

g) Face Processing

Among visual perception, nothing achieves such a special status in social interaction than faces. Faces are important for us to recognize others and to communicate with them, as facial expression is the biggest cue for us to "guess" individual's thoughts and feelings. Faces are so important in our "social being" position that we became experts in their perception, we process faces distinctly from any other visual stimulus, activating specific regions in the inferior temporal lobe: fusiform gyrus (including a region known as the fusiform face area (FFA) and the inferior and the medial occipital gyri (IOG/MOG) (Itier and Batty, 2009).

This expertise in face perception seems to be acquired specially through configural processing[5], as opposed to featural processing. Different conceptual models and levels of face processing are being defined, although this still is a controversial aspect. Here we will follow the relatively more consensual classification of configural processing by Maurer et al (2002):

1. Sensitivity to first-order relations: define faces by relations between its different components (two eyes above a nose, which is above a mouth).
2. Holistic processing: "glueing" the features to form a gestalt.
3. Sensitivity to second-order relations: distances between features.

According to this social and developmental impact of faces processing, several autism researchers have been testing and discussing this issue. Emotion perception is a profitable area within face processing in autism (Rose et al, 2007; Rutherford et al, 2008; Simmons et al, 2009), but it has stronger links with ToM. Here, we will circumscribe our discussion to the debate on autistic strategies of processing faces, where the perception of "whole" assumes a privileged position, in relation to the WCC account.

The first question is whether faces are as special to autistic individuals as they are to neurotypicals. A way to study that is through the face inversion effect. It is believed that inverting a face causes the disruption of holistic and configural processing, so that face turns to be processed more similarly to other objects, with featural or analytical processing enhancement (Rose et al, 2007; Annaz et al, 2009). Consequently, individuals with ASD were predicted to

[5] There is no agreement in what respects to the definition of configural processing which, in turn, leads to different classifications of face processing levels. For others perspectives about this issue see, for example, Annaz et al (2009) and Lopez et al (2004).

have reduced face inversion effects. Indeed, this prediction has been confirmed by most recent studies (Annaz et al, 2009). Another possible manipulation to test expertise of face processing is the use of thatcherized faces, which consists in face with inverted mouth and eyes. If this transformation looks extremely odd in upright faces, when inverting it, those differences are almost unnoticeable. This phenomenon is named “Thatcher Illusion” and essentially depends on face inversion effect. Rouse et al (2004) failed to prove less susceptibility of autistic individuals to “Thatcher illusion”, when compared with children with moderate mental retardation and typically developing children. Conversely, Nakahachi et al (2008) found that the autistic group, comparing to control group, was slower to differentiate a thatcherized face from a normal face when both presented uprightly; but had similar response times when both faces were inverted. The authors not only considered this a suggestion of less inverted face effect in autism, but go further claiming an holistic deficit in face processing, consistent with the hypotheses of a WCC in ASD.

However, to test if autistic individuals use a “featural” processing strategy instead of perceiving faces as “coherent wholes” another type of task might be used: the “whole-part” stimuli task. A target face is presented, below which are two faces (whole condition) or two features (part-condition), and the participant is required to identify which of the faces or features correspond to the target. A recent study (Annaz et al, 2009) made a cross-syndrome comparison (autism, Down syndrome and Williams syndrome) of holistic face recognition using this type of stimuli. Both the HFA and LFA groups found the part-condition easier than the whole condition. Surprisingly this was also the case of typically developing children, so it was considered that the part-whole effect was normal in ASD. Nevertheless, LFA group, which rarely take part on these experiments, had additional feature-specific effects, with disadvantage related to eyes and advantage to discrimination based on mouths. Lopez et al (2004) contradicts this data, showing similar performance across uncued featural trials (mouth, nose and eyes).

In this same study, both groups (ASD and control) were more accurate on the complete condition than the part condition, an effect known as the complete probe advantage (CPA), but only in the cue condition. Conversely, in the uncued condition, ASD were as accurately in the complete as they were in the part conditions (no CPA). The authors concluded that a lack of holistic processing, as suggested by weak central coherence, can be partially compensated with cues. One has, however, to note some subtle methodological differences across these studies, such as asynchronous timing of probe presentation. This introduces a memory component that renders direct comparisons difficult.

In relation to holistic face processing, Mooney face stimuli represent a quite unexplored paradigm in autism. In Mooney faces, we can not distinguish features, so neither the first stage nor the third stage of configural processing can be established (Latinus and Taylor, 2006) at least until the moment of detection. This leads us to relatively dominant holistic processing and, consequently Mooney faces would be valuable to determine impairment of this type processing in relation to the inversion effect. This is because, despite inversion effect being a solid proof of "face specialness", presumably it disrupts configural process only, and not the analytical process (Latinus and Taylor, 2005). That is, in Mooney faces we can not perceive the face by local segmentation and use of bottom-up processes (Farzin et al, 2009). Moreover, mooney faces are harder to recognize, comparing to photographic faces; are better identified when oriented upright; and are known to activate FFA (as reviewed by Farzin et al, 2009). Concluding, autistic perception of mooney faces might be an interesting area of research in autism to explore in the near future. Our laboratory has already preliminary data showing the value of Mooney stimuli in studying face inversion effects.

3. Electrophysiological Studies

The use of electrophysiology in autism has opened the door to the understanding of neural mechanisms underlying autistic behavioral impairments. In this paper, we focus our review to visual processing in ASD, despite the majority of electrophysiological studies in autism being dedicated to the auditory component.

Event-related potentials (ERP) from the cortical electroencephalogram are usually characterized as deflections reflecting associations between stimulus and response, which are labeled components of the ERP. This technique reveals both temporal and spatial nature of the complex brain activity, during a cognitive task. Hence it is quite natural to suppose that the wave components of ERPs from the electroencephalogram might reflect processing stages. Each component is characterized according to amplitude and latency, being labeled with a P when positive and with an N when negative. Latency traduces time needed for stimulus processing, while amplitude reflects how much processing is invested on a stimulus (Kemner and van Engeland, 2006). By the latency is possible to deduce if those components we attend to are early or later. Thus, although it depends on the type of task, we may generally consider-er that 100-200 ms (short-latency) reflects lower level processing and more than 200 ms (long-latency) represents intermediate to high level processing (Jeste and Nelson, 2009). As a result of several electrophysiological studies, specific waves have been defined and associated to certain cortical regions and a particular activity. The most important categorizations of ERPs waves with emphasis to visual perception are summarized in Table 1 (Jeste and Nelson, 2009; Sokhadze et al, 2009).

Table 1- ERPs waves in visual processing

Wave		Main Focus	Trigger
P300	P3a	Frontocentral area	Rare and task irrelevant stimuli (non-target novels in oddball paradigma). Reflects orienting and response to novelty
	P3b	Multiple dipole sources: hippocampus and parahippocampal areas, insula, temporal lobe, occipital lobe, thalamus	Response to a target or events that have importance to the subject. Reflects ability to sustain attention.
N100		Fronto-central cortex	Events salient to the individual. From the early infancy to young adulthood.
P100		ANT: frontal POST: fusyform gyrus	Facilitation of early sensory processing of attended stimuli.
N100		ANT: frontal POST: lateral extrastriate cortex + parieto-occipital + occipitotemporal areas	Attention-orienting towards task relevant stimuli.
N200/N2b		Centro-parietal	Categorization, perceptual closure and attention focusing.
P200/P2a		Inferior prefrontal	Working memory and attention. Task relevance of presented visual stimuli.
N290 (early infancy) N170 (later childhood)		Right hemisphere, posterior midline and paramidline electrodes	Encode physical features of the face. No recognition of a particular individual.
P400		Posterior lateral leads.	Face orientation and features.
N300		Amygdala and Prefrontal cortex	Increased allocation of attention to negative emotions (fearful or angry faces).

Besides being a totally non invasive technique and not requiring sedation, ERPs have their excellent temporal resolution as a major advantage. Consequently, they allow us to decodify putative neural mechanisms underlying cognition and behavior. Furthermore, we may found covert cognitive processing, not evident in overt behavior (Jeste and Nelson, 2009). However, this good temporal resolution is associated with a poor spatial resolution, that is, localization of ERP components is not very precise and relies on multiple assumptions. Nevertheless, when integrating ERPs with other tools such fMRI, reliable spatial descriptions can be accomplished (Corrigan et al, 2009). Another advantage, particularly in comparison to neuropsychological assessment, is that it requires minimal language and motor skill, being useful in younger and lower functioning autistic children (Webb et al, 2006; Jeste and Nelson, 2009).

In ASD, some consistent differences in ERPs are observed in comparison to normal population. In a study about visual processing impairments in autism (Sokhadze et al, 2009), three oddball visual stimuli were applied to test attention orienting, associated with anterior (frontal) topography, and sustained attention, related to centro-parietal (posterior) topography. At the anterior (frontal) topography, autistic individuals showed higher amplitudes and longer latencies of early components (P100, N100) and prolonged latencies for late components, such as P2a, N200 and P3a; this differences being more prominent at the right hemisphere. Specifically for P3a, longer latencies were only observed for novels and not for targets, in contrast with controls. Thus, the ASD group had more difficulty in processing distracters and orienting novelty. In addition to this, at the posterior topography longer latency of N100 and P2b plus lower amplitude of N2b were found in the ASD group, especially in the right hemisphere. Sokhadze et al (2009) concluded that in autism sensory inputs trigger larger potentials for both targets and distracters, because there is an overconnected network, with overprocessing to correctly distinct target from non-target novels. This speculation is in stark contradiction with the proposal of underconnectivity stemming from fMRI studies (see above). One may, nevertheless, link these findings with WCC, since attention to details, including those from the background noise, may result in impaired habituation to novelty and consequent overprocessing of non-target stimulus.

In visual perception, researchers have also been studying event related potentials elicited by Gabor stimuli. Milne et al (2009) described shorter latency of C1 and P1 in ASD comparing to controls, with no differences in amplitude. When decomposing its components they found in autistic population: (1) weaker but still significant increases in low alfa-band power approximately 300 msec after stimulus onset in or near the left cingulate gyrus, probably reflecting different task strategies (2) concerning components located in or near striate or extrastriate cortex, less spatial frequency dependent increases in α- and γ-power were observed in the ASD group than in the TD group suggesting less specialization of neural networks; (3) similar α- and β desynchronization in the parietal cortex, which may signify that release of inhibition related with attentional demands is not impaired in autism. To summarize, in this study no evidence of V1 hyper-activity was found, but neuro-integrative mechanisms at the perceptual level seem to be less efficient in ASD (Milne et al, 2009). Additionally, children with low-functionning autism had a lack of the 3rd harmonic component of their response to orientation-based texture and contour stimuli, and sweep threshold was twice as high as those of controls, reflecting a demand of higher coherence for significant neural response to textures (Pei et al, 2009). These studies have strong implications for the WCC account, as they put in evidence some degree of impairment in global integration in autistic populations. However, results are not consistent across different experiments, with some studies reporting normal-like activity (Kemner et al, 2007), so further investigation is needed.

Over the past decade, the bulk of experiments with ERPs in autistic populations is, in fact, related to face processing. Confirming data of neurocognitive tasks, no differences were observed in N170 latency to upright vs. inverted faces; that is, individuals with autism showed less inverted effect (McPartland et al, 2004). In the same study, the autism group exhibited longer N170 latency for faces, comparing to the typical group, but no difference in N170 latency for furniture. Moreover, McPartland and colleagues (2004) found that, in autism, slower left hemisphere N170 latency was associated with better face recognition ability. These results support the idea of different strategies and abnormal cortical specialization for faces perception in ASD, which might be explained by lack of experience due to lack of social motivation or to more profound abnormality in neural substrates (McPartland et al, 2004; Webb et al, 2006). Consequently, face processing impairment might be an early marker of autism, being present since early childhood. Indeed, Webb et al (2006) used ERPs to investigate face processing in 3-4 year old children with ASD compared with neurotypicals and children with developmental delay. The ASD group revealed slower responses to faces and a specific pattern of faster response to objects than faces, despite the unexpected observation of higher amplitude to faces. Both ASD and DD groups show no effects of hemisphere in amplitude of N170 precursor, an aspect also reported by Dawson et al (2005). In a recent research, Churches, Baron-Cohen and Ring (2009) proved that, in neurotypicals, not only faces have larger N170 than objects, but the amplitude was also dependent on objects characteristics, being greater as objects are more face-like. This should be considered a potential source of bias in future studies.

Face processing is undoubtly a privileged area of future research in autism, with great potential of clinical application. For example, it is being claimed as a possible functional trait marker of genetic susceptibility to autism (Dawson et al, 2005) and as an avenue to early intervention programs, so that rehabilitation of face processing strategies are incorporated in a critical period of development.

Finally, the study of direct and averted gaze in autistic populations is an interesting goal, since it combines both face processing and attention orienting components (Conty et al, 2007) and it is also taking relevance as one early behavioral characteristic of the broader autism phenotype (Elsabbagh et al, 2009).

4. IMAGING STUDIES

The development of imaging techniques in the last decades had an enormous impact in neurosciences research. Functional Magnetic Resonance Imaging (fMRI), in particular, produces spatial maps of brain activity, detected by changes in blood flow and blood oxygenation that cause signal fluctuations. Thus, fMRI provides a relatively good spatial resolution that lacks to ERP, and it is free from radiation exposure, as opposed to PET. However, it has some disadvantages too, such as: poor temporal resolution, making difficult the distinction of BOLD (Blood-oxygen-level dependent) responses to events that occur in a short time window; it is often very uncomfortable to the participant with acustic hypersensitivity, as is often the case in autism (Habib, 2000; Frith, 2003; Corrigan et al, 2009).

In what respects specifically to weak central coherence, few fMRI studies have directly tested this hypothesis. The first study with an ASD population evaluating performance in EFT (Ring et al, 1999) found generally greater activity in controls in the right dorsolateral prefrontal and bilateral dorsal parietal regions, and greater activity of the ventral occipitotemporal regions in ASD population. These results suggest that individuals with ASD and controls adopted different cognitive strategies during the task. Controls followed a normal strategy of serial search, involving higher order visual processing and working memory; while the autistic group made great use of mental imagery, with regions involved in object perception (Brodmann Areas 17, 18 and 19). Another intriguing observation in the autistic group was the right-sided activation of an area probably corresponding to MT/V5 (involved in motion perception). Manjaly et al (2007) improved this EFT experience by doubling the sample size (12 participants with ASD, as opposed to 6 in Ring et al, 1999); evaluating simultaneously behavioural performance and introducing a shape recognition task as baseline and a visuospatial control task requiring minimal local search, based in an EFT paradigm established by the same group of researchers (Manjaly et al, 2003). In this first experiment employed in adult healthy volunteers, Manjaly and colleagues (2003) found that left inferior and left superior parietal cortex as well as left ventral premotor cortex were significantly activated during EFT, contrasting with more widespread bilateral activations (parietal, occipital, cerebellar and frontal) while performing pure recognition of geometric shapes. So, when applying these findings to autism research (Manjaly et al, 2007) predicted that, according to WCC, autistic individuals would present attenuated right hemispheric activity and lateralization of activity to left intraparietal sulcus and left inferior frontal gyrus, since these areas were found to be implicated in local stimulus processing. Moreover, they admitted that the results of this study would help to address the question of distinct neurophysiological underpinnings between WCC and EPF. The initial predictions in favour of WCC were not confirmed, instead the autistic group, comparing to control group, showed activations in the cortex surrounding the right calcarine sulcus and in extrastriate cortex bilaterally, which according to the authors is accounted for by the EPF theory. Finally, a third study used fMRI during EFT performance this time in pre-adolescents with ASD (Lee et al, 2007b), contrasting with the adult population of Ring et al (1999) and the adolescent participants in Manjaly et al (2007) study. Since hemispheric specialization and executive functions are still immature in pre-adolescents children, Lee and colleagues (2007b) tackled these questions using a unique self-paced design to ensure that fMRI results represent processes actually implicated in solving the task. Control children activated frontal cortex exclusively in the left hemisphere, including dorsolateral, medial and dorsal premotor areas, additionally a bilateral activation of ventral temporal cortex was observed. In contrast, ASD children had little recruitment of prefrontal and ventral temporal areas, only activating dorsal premotor cortex; but showed superior activation of left parietal and right occipital cortex. Lee and colleagues (2007b) concluded that the findings of reduced prefrontal involvement in ASD "reveal a neural basis for weak central coherence as a processing style in ASD children" (p.192), although the superior activation in occipital cortex also favors the EPF account.

So, what can we conclude from these three studies with EFT performance in ASD? Three consistent findings are present in those researches: (1) autistic individuals have lesser activation of the working memory system; (2) control group had broader bilateral activation of temporo-parietal regions; (2) autistic individuals show greater activation of the visual cortex. The first two aspects suggest a "weak top down control" in the autistic group, with performance in

EFT being much more dependent of local visual processing. These characteristics can be accounted for by the WCC theory. The obstacle pointed out by Manjaly et al (2007) is related with lateralization of global/local processing, since it has been suggested a right hemisphere bias for global processing and a left hemisphere bias for local processing (Fink et al, 1997; Han et al, 2002). However, this hemispheric asymmetry for global/local process is not observed in some studies, at least in all stages of visual cortical analysis or in all the conditions applied (Heinze et al, 1998; Billington et al, 2008) Besides EFT, earlier in this paper we mentioned another task in which autistic individuals often have superior performance: the block design test (BDT). Additionally, it was proven that BDT is a good task to evaluate locally oriented visual processing (Caron et al, 2006). Bölte et al (2008) used fMRI to investigate the neurofunctional basis in ASD of this peak performance in Wechsler Intelligence Scales. They found reduced activation in right V2v (ventral) in the autism group comparing with the control group and suggested five possible explanations for this phenomenon:

1. Decreased efforts to recognize and segment the visual stimuli
2. Reduced drive for gestalt perception
3. Decreased top-down control with the adoption of a bottom-up strategy
4. Impaired feedback between V2 and V1/V3.
5. Altered perception at an early stage, e.g. the parvocellular pathway

There is however a major interpretation problem: V2v (ventral) represents the upper visual field. Why would a specific visual field show differential changes in response? This suggests that eye movements or differential deployment of attention might be contributing to these observations. In any case, if the data is valid, the second and third aspects would favor the weak central coherence account, while the last one could potentially accounting for enhanced perceptual functioning. However, it is also important to considerer some limitations of this study while interpreting the results. The sample size was small (seven individuals with

HFA), including only males adolescents and adults. Furthermore, as stated above, oculomotor abnormalities are frequent in autism, in particular elevated saccade frequency (Brenner et al, 2007), so it would be important to include an eye-tracking device in this experiment to exclude influence of eye movement in the fMRI results.

In fact, no other imaging studies directly addressing the WCC account are found to date in the present literature. However, an aspect that we have already explored in the context of global vs. local perception is face processing and this is an issue that has attracted several fMRI researchers in the last years. Some studies of face perception in ASD described lower activation of the fusiform face area (FFA) (Schultz et al, 2000; Pierce et al, 2001; Hubl et al, 2003; Humphreys et al, 2008; Corbett et al, 2009) and greater signal in inferior temporal gyrus (Schultz et al, 2000) and medial occipital gyrus (Hubl et al, 2003), areas normally related to object perception. According to these findings it was speculated that face processing was performed with a featural-based strategy, with a predisposition to local rather than global processing, which would be consistent with the WCC theory (Schultz et al, 2000; Hubl et al, 2003). However alternative explanations to these results can be envisaged, namely a decreased interest in analyzing faces, with ensuing lower activation of the fusiform face area. Lower activation of the fusiform region was also reported in unaffected siblings of individuals with autism, but restricted to right hemisphere as opposed to bilateral in autistic individuals (Dalton et al, 2007). In contrast, other researchers refer no hypoactivation of FFA (Hadjikhani et al, 2004; Kleinhans et al, 2008) or found that this activation was likely to be explained by certain variables such as the time spent fixating the face stimuli (Dalton et al, 2005) or face familiarity (Pierce et al, 2004; Pierce et al, 2008). The latter study did, indeed, show normal fusiform activity in children with autism when viewing a face of their mother or other children, but not when looking at stranger adult faces. The authors concluded that a selective fusiform deficit in response only to the faces of adult strangers might be the result of reduced attention and interest during those conditions**.**, In fact even the patients' favorite cartoons are able to activate FFA better than faces (Grelotti et al, 2005). Bookheimer et al (2008) used fMRI to study the inverted face effect in ASD, which we have mentioned earlier as a way of disrupting holistic processing, and found few susceptibility to this effect in the autistic group, but an unexpected increased activation of FFA, similar to control group. Differences in activation between both groups were found in prefrontal cortex and amygdala. The authors have, therefore, concluded that behavioural differences in this case were not related to visual processing, but to the social meaning of the stimuli.

A strikingly approach of these contradictory results was made by Klin (2008) when pointing out three things that researchers in this area should keep in mind: (1) it is fundamental to use eye-tracking, not only to measure visual attention but also to ensure that results are not influenced by abnormal visual fixation patterns; (2) high level factors such as arousal and motivation may modulate activation of relay structures at the earliest points of the visual stream, which justifies that fMRI studies should be whole brain and not restricted to regions of interest such as the fusiform gyrus; (3) it should be taken into consideration that fusiform gyrus may not be exclusively related to face processing, since its activation has been observed for non-face stimuli such as objects for which the subjects are experts and stimuli conveying visual social interactions..

Finally, some authors have been hypothesized that impairments of face perception in autism are consequence of top-down processes and abnormal connectivity between FFA and the limbic system (Kleinhans et al, 2008; Pierce et al, 2008). In the study of Pierce et al (2008) increased functional connectivity was found between the right fusiform region and the right amydgala. This result is at odds with the underconnectivity theory.

Concerning structural connectivity, diffusion-tensor imaging (DTI) allows to extract fractional anisotropy (FA), a measure of orientational coherence raging from 0 (isotropic) to 1 (anisotropic), and mean diffusivity (MD), which provides *in vivo* information of white matter organization (Kleinhans et al, 2008; Ke et al 2009). The first study applying DTI to autism research (Barnea-Goraly et al, 2004) relates lower FA in structures involved in mentalizing and emotional processes (ventromedial prefrontal cortices, anterior cingulate gyri, temporoparietal junctions, superior temporal sulcus and amygdala), as well as face and gaze processing (left optic radiation extending to fusiform gyrus). In this same study, it was also found a decreased FA in the corpus callosum, reflecting disordered hemispheric communication, which was confirmed further by Alexander et al (2006) in a research specifically directed to this region. Alexander et al (2006) identified a smaller corpus callosum volume positively associated with lower mean FA, however, they observed that this did not extend to all the autism subgroups. Lower FA and higher MD were found in a subgroup of ASD individuals that had an inferior mean verbal performance and full IQ scale, but not diverging from the other subgroup in terms of autism severity. On the other hand, Ke et al (2009) report a positive correlation between FA value in right frontal lobe and total score of CARS (childhood autism rating score). Lower FA accompanied by higher MD and radial diffusity in autism has also been reported in temporal lobe regions, e.g. superior temporal gyrus and temporal stem (Lee et al, 2007a). Sundaram et al (2008) contradicted one of the principles in the EPF model (Mottron et al, 2006) when demonstrating low FA and high diffusivity of the short association fibers in ASD, meaning no evidence of excessive short range connectivity. Ben Bashat and colleagues (2007) used DTI to study white matter maturation in young children with autism and found higher FA more dominant in left hemisphere and, particularly, in the frontal lobe.

Concerning structural findings in autism, many open questions still remain such as the status of synaptic pruning in particular circuits (not directly assessed by current techniques). It also remains to be tested whether there is an imbalance between the maturation of feedback (top-down) versus feed-forward (bottom-up) systems (Hill and Frith, 2003). Ke et al (2009) pointed out some of the available findings of diffuse changes in neural connectivity or gray matter integrity, trough fMRI, DTI and VBM (Voxel Based Morphometry) studies, as providing a putative neurobiological level interpretation of WCC. Data driven approaches need to be combined with such model driven considerations, in order to establish a solid theoretical framework to explain the cognitive deficits in autism.

DISCUSSION

In the light of this revision paper, we might conclude that, despite the effort put in autism investigation specifically in what respects to visual spatial abilities and WCC, no consensus was achieve so far. However, the bulk of the results point through a local processing bias or an impairment to perceive the global framework, although the reduced global processing might be just a corollary epiphenomenon of superior local processing. Thus, Happé and Frith (2006) have argued for the need for tests clearly tapping global and local processing independently. The majority of the studies have suggested superior performance of autistic children in BD and EFT, two classical tests of WCC, but their relation to putative superior local visual processing remains to be clarified. Less consensual are the results of studies applying visual illusions and Navon figures to test the hypothesis of a local bias in ASD. Conversely, evidence in favor of the WCC account was also put forward by demonstrations of the role of contextual influence and impaired global perception when autistic subjects perceive impossible and fragmented figures,.

However, it will be difficult to put a decisive test to the theory just based on behavioural data. In the domain of electrophysiology, few studies have been performed in visual processing, but results are generally in favor of a different pattern of performance in ASD. However, most studies did not control for eye movements or concomitant behavioral performance. Another technique, with auspicious results, that has been applied in autism research, is fMRI. Only a few fMRI studies have directly addressed WCC and concurred in showing an alternative processing style or cognitive strategy in ASD population when compared with neurotypicals, though the interpretation of the results varied across those studies. On the other hand, face processing, due to its specialness in human social interaction, has been proven to be an important research target, with neuropsychological, ERPs and fMRI studies supporting the use of a more featural-based strategy by autistic individuals.

However, the actual drawback of WCC account is the lack of neurobiological basis. This question has been approached in two different ways: (1) considering a deficit in a specific pathway; (2) regarding for diffuse changes in neuronal connectivity. The first option, closely related to EPF theory, suggests an impaired processing in afferent magnocellular pathways or its target dorsal stream. A considerable number of attempts have been made to prove this hypothesis, including various studies involving visual motion stimuli, but results are mixed with some reporting high motion coherence thresholds in autism and others showing no differences in comparison to neurotypicals. The second approach represents an extension of WCC to the Underconnectivity Theory, which defends a deficit in the integrative circuitry at a higher level with less functional connectivity between various cortical areas. This account offers an explanation for both executive and social impairments in autism and benefits from growing evidence through fMRI and DTI studies that proved lack of functional connectivity in autism. However, this theory lacks specificity and, in fact, several counterexamples of excess long range functional and structural connectivity have been found, and also reported in this thesis. Finally, a definite proof of the role of synchrony will depend on accurate measurements at the millisecond time scale, which is only achieved with EEG and not with fMRI, which has a temporal resolution of several seconds. Indeed the finest time scale of neuronal events is beyond the capabilites of MR techniques and the best one can do is to perform coarse correlation analysis. Recent techniques addressing the role of causality and extending neurochronometry into finer time scales are changing this scenario.

The second point of debate is why do we find diverging results when investigating WCC in autism? What are the possible *biases* and how can researchers overcome it? Eye movements are widely reported as an important influence in the results of visual processing studies, justifying the regular coregistration of eye-tracking measures. Oculomotor abnormalities are related to another common problem in autistic population: attention (Brenner et al, 2007). This is particular important in psychophysical, ERP and fMRI studies using moving stimuli/dynamic patterns, when attentional deficits, rather than WCC, might be assumed as the underlying cause of high perceptual thresholds or abnormal responses (Dakin & Frith, 2005). Besides eye movements, performing a specific task to control attentional demand, employing adaptive psycophysical procedures, using short duration stimulus or adding control cues, are some of the solutions proposed to decrease the influence of attentional drifts in the observed responses. Specifically in face perception tasks, motivation along with lack of interest in non familiar faces may also be confounds that researchers should consider in the interpretation of their results (Klin et al, 2008; Annaz et al, 2009). The composition of the clinical group is also a methodological problem frequently discussed in autism research. First, few studies have been performed in LFA, due to difficulty in applying the most common tasks and investigation techniques. This aspect represents a gap in ASD research, as impairments are more severe and particularly pervasive in LFA individuals. On the other hand, many studies include in the same group participants from a wide range of autistic spectrum disorders, mostly Asperger's Syndrome and HFA, and interpret the results as if they were a unique disorder. However, few studies testing separately those two groups showed quite distinct patterns of results, with Asperger's Syndrome being significantly less impaired (Jolliffe and Baron-Cohen, 2001; Tsermentseli et al, 2008). Thus, when treating the ASD as a unique disorder, researchers might introduce a confounding and uninterpretable *bias* in the overall results.

Two core questions must be answered when evaluating the relevance of WCC account: are a local *bias* and/or a weaker drive for coherence specific features in autism? And are they present in all autistic individuals (universality)? To address the first question several studies have compared autistic performance in WCC tasks with other clinical groups, such as schizophrenia and depression (Bölte et al, 2007), dyslexia (Tsermentseli et al, 2008), Williams

Syndrome (Annaz et al, 2009) and right hemisphere damage (reviewed by Happé and Frith, 2006). Indeed, all these groups share, at least in some studies, a tendency to detail-focused processing. However, the same behavior may not reflect common neurobiological abnormalities and more research efforts are needed to clarify the links between those groups. Additionally, we must notice that co-morbid disorders such as attention deficit disorder, dyslexia, epilepsy and motor coordination deficits are present in a significant part of autistic population (Frith, 2003; Geshwind, 2009). In what respects to universality, many researchers admit that WCC may be present in only a subset of the ASD population (e.g. Jarrold & Russell, 1997; Milne et al, 2002; Burnette et al, 2005; Noens & van Berckelaer-Onnes, 2005). Happé & Frith (2006) argue that the tasks applied were indirect measures of WCC and, consequently, there are many ways both to pass and fail the test. Besides, the ASD spectrum presents considerable heterogeneity which contributes to different results across this population.

Along these lines, is precisely this heterogeneity characteristic of ASD that leads some authors to believe that the behavioural fractionation of social impairment, deficits in communication and stereotyped/repetitive pattern of behavior may reflect a conjugation of distinct underlying causes at genetic, cognitive and neural levels. That is, perhaps it is "time to give up on a single explanation for autism" as argued by Happé, Ronald and Plomin (2006). Pellicano et al (2006), although confirming support for WCC at the visual-spatial domain, failed to confirm a single inter-individual processing style. In both studies, low correlations between the three core symptomatic areas and three core theories of autism (WCC, ToM, ED) were found, even if a few exceptions can be arguably put forward. In what respects to the "fractionation" of neural substrate for ASD, Happé & Ronald (2008) considered that the best candidate to justify non-social and social impairments is an abnormal top-down modulation associated with low functional connectivity. Similar mechanisms have been proposed for other neuropsychiatric conditions, and the current challenge is to find more specific mechanisms.

Accordingly, at a genetic level, it would be more profitable to search for ASD susceptibility genes associated with specific behavioral patterns, rather than with autism as a whole.

The search for an explanation to autism is far from being a lost cause. Understanding the core deficits of autism at a cognitive and neural level will have great impact in diagnostic and therapeutic domains, contributing to adopt the best behavioral strategies for rehabilitation.

CONCLUSION

Several behavioural, electrophysiological and imaging studies do provide some support for a revised WCC account in ASD. However, the neural basis of this local oriented processing, or difficulty in achieving a global cognitive framework, in autism continues to be poorly understood and it is imperative to clarify the links between various theories that have been proposed to date. In such a challenge condition as autism, and whether WCC is a dominant piece or must be integrated with other deficits, a great deal of research is still necessary to “get the puzzle done”.

ACKNOWLEDGMENTS

I am grateful to Professor Miguel Castelo-Branco for accepting the orientation of this paper and guiding me in the neurosciences domain, which before this work constituted a mystery for me. Thank you for the precious help outlining the subject and defining clear objectives and for the final revision enriched with new data.

I would like to thank to Professora Paula Tavares for the meticulous and careful revision of my work, for the useful introductory concepts, particularly in what respect to face processing, and for giving me assess to several papers used in this review.

For those, in my life, who are my source of inspiration and multidimensional knowledge, and always offer unconditional support in this journey, my profound thanks.

REFERENCES

Alexander AL, Lee JE, Lazar M, Boudos R, DuBray MB, Oakes TR, Miller J, Lu J, Jeong E, McMahon W, Bigler E, Lainhartd JE (2007) Diffusion tensor imaging of the corpus callosum in autism. NeuroImage. 34:61–73. Castelo-Branco M, Formisano E, Backes W, Zanella F, Neuenschwander S, Singer W, Goebel R (2002) Activity patterns in human motion-sensitive areas depend on the interpretation of global motion. Proc Natl Acad Sci. 99(21):13914-9.

Annaz D, Karmiloff-Smith A, Johnson M, Thomas M (2009) A cross-syndrome study of the development of holistic face recognition in children with autism, Down syndrome, Williams syndrome. Journal of Experimental Child Psychology. 102: 456-486

Ashwin E, Ashwin C, Rhydderch D, Howells J, Baron-Cohen S (2009) Eagled-Eyed Visual Acuity: An experimental Investigation of Enhanced Perception in Autism. Biological Psychiatry. 65: 17-21

Bach M & Dakin S (2009) Regarding “Eagle-Eyed Visual Acuity: An Experimental Investigation of Enhanced Perception in Autism”. Biological Psychiatry. 66(10):e19-e20

Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL, (2004) White matter structure in autism: preliminary evidence from diffusion tensor imaging. Biol. Psychiatry. 55:323–326

Baron-Cohen S (2002) The extreme male brain theory of autism. Trends in Cognitive Sciences. 6(6):248-254

Baron-Cohen S, Belmonte M (2005) Autism: a window onto the development of the social and the analytic brain. Annu. Rev. Neurosci. 28: 109-126

Baron-cohen S, Leslie A, Frith U (1985) Does the autistic children have a "theory of mind"? Cognition. 21:37-46.

Bear MF, Connors BW, Paradiso MA (2006). Neuroscience: Exploring the Brain. 3rd Edition. Philadelphia: Lippincott.

Ben Bashat D, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, Even A, Levy Y, Ben Sira L. (2007) Accelerated maturation of white matter in young children with autism: a high b value DWI study. Neuroimage. 37(1):40-7.

Bertone A, Mottron L, Jelenic P, Faubert J (2003) Motion Perception in Autism: A "Complex" Issue. Journal of Cognitive Neuroscience. 15(2):218-225

Best C, Moffat V, Power M, Owens D, Johnstone E (2008) The Boundaries of the cognitive phenotype of autism: theory of mind, central coherence and ambiguous figure perception in young people with autistic traits. Journal of Autism and Development Disorders 38:840-847

Billington J, Baron-Cohen S, Bor D (2008) Systemizing influences attentional processes during the Navon task: an fMRI study. Neuropsychologia. 46(2):511-20.

Bölte S, Holtmann M, Poustka F, Scheurich A, Schmidt L (2007) Gestal perception and local-global processing in high-functioning autism. Journal of Autism and Development Disorders 37:1493-1504

Bölte S, Hubl D, Dierks T, Holtmann M, Poustka F (2008) An fMRI-study of locally oriented perception in autism: altered early visual processing of the block design test. J Neural Transm. 115(3):545-52

Bookheimer SY, Wang AT, Scott A, Sigman M, Dapretto M (2008) Frontal contributions to face processing differences in autism: evidence from fMRI of inverted face processing. J Int Neuropsychol Soc. 14(6):922-32.

Brenner L, Turner K, Müller RA (2007) Eye movement and visual search: are the elementary abnormalities in autism. Journal of Autism and Development Disorders. 37: 1289-1309

Burnette CP, Mundy PC, Meyer JA, Sutton SK, Vaughan AE, Charak D (2005) Weak central coherence and its relations to theory of mind and anxiety in autism. Journal of Autism and Developmental Disorders 35(1): 63-73

Caron MJ, Mottron L, Berthiaume C, Dawson M (2006) Cognitive mechanisms, specificity and neural underpinnings of visuospatial peaks in autism. Brain. 129(7):1789-1802

Castelli F, Frith C, Happé F, Frith U (2002) Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes . Brain. 125(8):1839-1849

Castelo-Branco M, Goebel R, Neuenschwander S, Singer W (2000) Neural synchrony correlates with surface segregation rules. Nature. 405(6787):685-689

Castelo-Branco M, Mendes M, Sebastião AR, Reis A, Soares M, Saraiva J, Bernardes R, Flores R, Pérez-Jurado L, Silva E (2007) Visual phenotype in Williams-Beuren syndrome challenges magnocellular theories explaining human neurodevelopmental visual cortical disorders. The Journal of Clinical Investigation. 117(12):3720-9.

Castelo-Branco M, Mendes M, Silva F, Massano J, Januário G, Januário C, Freire A (2009) Motion integration deficits are independent of magnocellular impairment in Parkinson's disease. Neuropsychologia. 47(2):314-20.

Castelo-Branco M, Mendes M, Silva MF, Januário C, Machado E, Pinto A, Figueiredo P, Freire A (2006) Specific retinotopically based magnocellular impairment in a patient with medial visual dorsal stream damage. Neuropsychologia. 2006;44(2):238-53

Cherkassky VL, Kana R, Keller TA, Just MA (2006) Functional connectivity in a baseline resting-state network in autism. Neuroreport. 17(16):1687-90.

Churches O, Baron-Cohen S, Ring H (2009) Seeing face-like objects:an event-related potential study. 20(14): 1290-1294

Conty L, N'Diaye K, Tijus C, George N (2007) When eye creates the contact! ERP evidence for early dissociation between direct and averted gaze motion processing. Neuropsychologia. 45: 3024-3037

Corbett BA, Carmean V, Ravizza S, Wendelken C, Henry ML, Carter C, Rivera SM (2009) A functional and structural study of emotion and face processing in children with autism. Psychiatry Res. 173(3):196-205.

Corrigan N, Richards T, Webb S, Murias M, Merkle K, Kleinhans N, Johnson LC, Poliakov A, Aylward E, Dawson G (2009) An Investigation of the Relationship Between fMRI and ERP Source Localized Measurements of Brain Activity during Face Processing. Brain Topogr.22:83–96

Crewther D & Sutherland A (2009) The More He Looked Inside, the More Piglet Wasn't There: Is Autism Really Blessed with Visual Hyperacuity? Biological Psychiatry. 66(10):e21-e22

Dakin S and Frith U (2005) Vagaries of visual perception in autism. Neuron. 48: 497-507.

Dalton K, Nacewicz B, Alexander A, Davidson R (2007) Gaze-fixation, brain activation, and amygdala volume in unaffected siblings of individuals with autism. Biological Psychiatry. 61:512–520

Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, Alexander AL, Davidson RJ (2005) Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 8(4):519-26.

Dawson G, Webb S, Wijsman E, Schellenberg G, Estes A, Munson G, Faja S (2005) Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. Development and Psychopathology. 17:3:679-697

Del Viva MM, Igliozzi R, Tancredi R, Brizzolara D (2006) Spatial and motion integration in children with autism. Vision Research. 46:1242–1252

Edgin JO, Pennington BF (2005) Spatial cognition in autism spectrum disorders: superior, impaired, or just intact? Journal of Autism and Development Disorders 35(6): 729-745

Elsabbagh M, Volein A, Csibra G, Holmboe K, Garwood H, Tucker L, Krljes S, Baron-Cohen S, Bolton P, Charman T, Baird G, Johnson MH (2009) Neural Correlates of Eye Gaze Processing in the Infant Broader Autism Phenotype. Biological Psychiatry. 65:31–38

Farzin F, Rivera SM, Whitney D (2009) Holistic crowding of Mooney faces. Journal of Vision. 9(6):18, 1–15

Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ (1997) Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. Brain. 120 (10), 1779–1791.

Frith U (2003) Autism: explainning the enigma. 2nd Edition. Oxford: Blackwell Publishing

Frith U, Frith CD (2003) Development and neurophysiology of mentalizing. Phil. Trans. R. Soc. Lond. 358: 459-473

Frith U, Happé F (1994) Autism: beyond theory of mind. Cognition 50: 115-132

Geschwind D (2009) Advances in autism. Annual Review of Medicine. 60: 367-380

Grelotti DJ, Klin AJ, Gauthier I, Skudlarski P, Cohen DJ, Gore JC, Volkmar FR, Schultz RT (2005) fMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. Neuropsychologia. 43(3):373-85

Habib M (2000) Bases Neurológicas dos Comportamentos. 1ª Edição. Climepsi Editores

Hadjikhani N, Joseph RM, Snyder J, Chabris CF, Clark J, Steele S, McGrath L, Vangel M, Aharon I, Feczko E, Harris GJ, Tager-Flusberg H (2004) Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. Neuroimage. 22(3):1141-50

Han S, Weaver JA, Murray SO, Kang X, Yund EW, Woods DL (2002) Hemispheric Asymmetry in Global/Local Processing: Effects of Stimulus Position and Spatial Frequency. NeuroImage. 17:1290–1299

Happé F (1996) Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. J Child Psychol Psychiatry. 37(7):873-7

Happé F, Booth RD (2008) The power of positive: revisiting weak central coherence in autism spectrum disorders. The Quarterly Journal of Experimental Psychology 61(1): 50-63

Happé F, Frith U (2006) The weak central coherence account: detail-focused cognitive style in autism spectrum disorders. Journal of Autism and Development Disorders 36(1): 5-25

Happé F, Ronald A (2008) The “fractionable autism triad”: a review of evidence from behavioural, genetic, cognitive and neural research. 18: 287-304

Happé F, Ronald A, Plomin R (2006) Time to give up on a single explanation for autism. Nature Neuroscience 9(10): 1218-220

Heinz HJ, Hinrichs H, Scholz M, Burchert W, Mangun R (1998) Neural mechanisms of global and local processing: a combined PET and ERP study. J. Cogn. Neurosci. 10:485-498.

Hill E (2004) Executive dysfunction in autism. Trends in Cognitive Sciences. 8(1): 26-32

Hill E, Frith U (2003) Understanding autism: insights from mind and brain. Phil. Trans. R. Soc. Lond. 358: 281-289

Hubert B, Wicker B, Moore D, Monfardini E, Duverger H, Da Fonseca D, Deruelle C (2007) Brief Report: Recognition of Emotional and Non-emotional Biological Motion in Individuals with Autistic Spectrum Disorder. J Autism Dev Disord. 37:1386–1392

Hubl D, Bölte S, Feineis-Matthews S, Lanfermann H, Federspiel A, Strik W, Poustka F, Dierks T (2003) Functional imbalance of visual pathways indicates alternative face processing strategies in autism. Neurology. 61(9):1232-7.

Humphreys K, Hasson U, Avidan G, Minshew N, Behrmann M (2008) Cortical patterns of category-selective activation for faces, places and objects in adults with autism. Autism Res. 1(1):52-63

Iarocci G, Burack JA, Shore DI, Mottron L, Enns JT (2006) Global-local visual processing in high functioning children with autism: structural vs. implicit task biases. Journal of Autism and Development Disorders 36(1): 117-129

Itier R, Batty M (2009) Neural bases of eye and gaze processing: The core of social cognition. Neuroscience & Biobehavioral Reviews. 33(6):843-863

Jarrold C, Russell J (1997) Counting abilities in autism: possible implications for central coherence theory. Journal of Autism and Development Disorders 27(1): 25-37

Jeste SS, Nelson CA 3rd (2009) Event related potentials in the understanding of autism spectrum disorders: an analytical review. J Autism Dev Disord. 39(3):495-510

Jollife T, Baron-Cohen S (1997) Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? J Child Psychol Psychiatry. 38(5):527-34.

Jollife T, Baron-Cohen S (2001) A test of central coherence theory: Can adults with high-functioning autism or Asperger syndrome integrate fragments of an object?. Cognitive Neuropsychiatry. 6:193-216

Just MA, Cherkassky VL, Keller TA, Kana R, Minshew NJ (2007) Functional and anatomical cortical underconnectivity in autism: evidence from na fMRI study of na executive function task and corpus callosum morphometry. Cerebral cortex. 17:951-961

Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004) Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain 127: 1811-1821

Kanner L (1943) Autistic disturbances of affective contact. Nervous Child. 2: 217-250

Ke X, Tang T, Hong S, Hang Y, Zou B, Li H, Zhou Z, Ruan Z, Lu Z, Tao G, Liu Y (2009) White matter impairments in autism, evidence from voxel-based morphometry and diffusion tensor imaging. Brain Res. 1265:171-7.

Kemner C, Lamme VA, Kovacs I, van Engeland H (2007) Integrity of lateral and feedback-ward connections in visual processing in children with pervasive developmental disorder. Neuropsychologia. (45) 1293-1298.

Kemner C, van Engeland H (2006) ERPs and Eye Movements Reflect Atypical Visual Perception in Pervasive Developmental Disorder. Journal of Autism and Developmental Disorders. 36(1):45-54

Kleinhans NM, Richards T, Sterling L, Stegbauer KC, Mahurin R, Johnson LC, Greenson J, Dawson G, Aylward E (2008) Abnormal functional connectivity in autism spectrum disorders during face processing. Brain. 131(4):1000-12

Klin A (2008) Three things to remember if you are a functional magnetic resonance imaging researcher of face processing in autism. Biol Psychitary. 64:549-551

Klin A, Lin D, Gorrindo P, Ramsay G, Jones W (2009) Two-year-olds with autism orient to non-social contingencies rather than biological motion. Nature. 459:257-293

Knickmeyer R, Baron-Cohen S, Raggatt P, Taylor K (2005) Foetal testosterone, social relationships, and restricted interests in children. Journal of Child Psychology and Psychiatry. 46(2):198–210.

Koshino H, Kana R, Keller TA, Cherkassy VL, Minshew N, Just MA (2008) fMRI Investigation of Working Memory for Faces in Autism: Visual Coding and Underconnectivity with Frontal Areas. Cerebral Cortex. 18(2):289-300

Latinus M, Taylor M (2005) Holistic Processing of Faces: Learning Effects with Mooney Faces. Journal of Cognitive Neuroscience. 17(8):1316-1327

Latinus M, Taylor M (2006) Face processing stages: Impact of difficulty and the separation of effects. B rain Research. 1123:179–187

Lee JE, Bigler ED, Alexander AL, Lazar M, DuBray MB, Chung MK, Johnson M, Morgan J, Miller JN, McMahon WM, Lu J, Jeong EK, Lainhart JE (2007a) Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. Neurosci Lett. 424(2):127-32

Lee P, Foss-Feig J, Henderdon JG, Kenworthy L, Gilotty L, Gaillard WD, Vaidya C (2007b) Atypical neural substrates of Embedded Figures task performnace in children with Austism Spectrum Disorder. Neuroimage. 38:184-193.

López B, Donnelly N, Hadwin JA, Leekam SR (2004) Face processing in high-functioning adolescents with autism: evidence for weak central coherence.Visual Congnition 11(6): 673-688

Manjaly ZM, Bruning N, Neufang S, Stephan KE, Brieber S, Marshall JC, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Konrad K, Fink GR. (2007) Neurophysiological correlates of relatively enhanced local visual search in autistic adolescents. Neuroimage. 35(1):283-91.

Manjaly ZM, Marshall JC, Stephan KE, Gurd JM, Zilles K, Fink GR (2003) In search of the hidden: an fMRI study with implications for the study of patients with autism and with acquired brain injury. NeuroImage. 19:674–683.

Maurer D, Grand RL, Mondloch CJ (2002) The many faces of configural processing. Trends Cogn. Sci. 6:255–260.

McPartland J, Dawson G, Webb SJ, Panagiotides H, Carver LJ(2004) Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J Child Psychol Psychiatry.45(7):1235-45

Milne E, Scope A, Pascalis O, Buckley D, Makeig S (2009) Independent component analysis reveals atypical electroencephalographic activity during visual perception in individuals with autism. Biol Psychiatry. 65(1):22-30

Milne E, Swettenham J, Hansen P, Campbell R, Jeffries H, Plaisted K (2002) High motion coherence thresholds in children with autism. Journal of Child Psychology and Psychiatry 43(2): 255-263

Mitchell P, Ropar D (2004) Visuo-spatial abilities in autism: a review. Infant and Child Development. 13: 185–198

Mizuno A, Villalobos ME, Davies MM, Dahl BC, Müller RA (2006) Partially enhanced thalamocortical functional connectivity in autism. Brain Research. 1104(1): 160–174.

Mottron L , Belleville S, Ménard E (1999) Local Bias in Autistic Subjects as Evidenced by Graphic Tasks: Perceptual Hierarchization or Working Memory Deficit? Journal of Child Psychology and Psychiatry. 40:743-755

Mottron L and Burack J (2001) Enhanced perceptual functioning in the development of autism. In: The development of autism: perspectives from theory and research (Burack et al, ed), pp149-169. Mahwah, NJ: Lawrence Erlbaum

Mottron L, Dawson M, Soulières I, Hubert B, Burack J (2006) Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. Journal of Autism and Development Disorders. 36(1): 27-42

Nakahachi T, Yamashita K, Iwase M, Ishigami W, Tanaka C, Toyonaga K, Maeda S, Hirotsune H, Tei W, Yokoi K, Okajima S, Shimizu A, Takeda M (2008) Disturbed holistic processing in autism spectrum disorders verified by two cognitive tasks requiring perception of complex visual stimuli. Psychiatry Research 159: 330-338

Navon D (2008) A single-element impact in global/local processing: the roles of element centrality and diagnosticity. Psychological Research. 72:155–167

Noens I, van Berckelaer-Onnes I (2005) Captured by details: sense-making, language and communication in autism. Journal of Communication Disorders. 38: 123-141

Pei F, Baldassi S, Procida G, Igliozzi R, Tancredi R, Muratori F, Cioni G (2009) Neural correlates of texture and contour integration in children with autism spectrum disorders.

Vision Research. 49: 2140–2150

Pellicano E, Gibson L, Maybery M, Durkin K, Badcock D (2005) Abnormal global processing along the visual pathway in autism. Neuropsychologia. 43: 1044-1053

Pellicano E, Maybery M, Durkin K, Maley A (2006) Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: “weak” central coherence and its relationship to theory of mind and executive control. Development and Psychopathology 18: 77-98

Pierce K, Haist F, Sedaghat F, Courchesne E (2004) The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain. 127(12):2703-16.

Pierce K, Müller RA, Ambrose J, Allen G, Courchesne E (2001) Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. Brain. 124(10):2059-73.

Pierce K, Redcay E (2008) Fusiform function in children with an autism spectrum disorder is a matter of "who". Biol Psychiatry. 64(7):552-60.

Plaisted K, Swettenham J, rees L (1999) Children with autism show local precedence in a divided attention task and global precedence in selective attention task. J. Child Psychol. Psychiat. (5):733-742

Plaisted, K (2001) Reduced Generalization in autism: an alternative to weak central coherence. In: The development of autism: perspectives from theory and research (Burack et al, ed), pp149-169. Mahwah, NJ: Lawrence Erlbaum

Polyak SL (1941) The Retina. University of Chicago Press, Chicago.

Ring H, Baron-Cohen S, Whellwright S, Williams S, Brammer M, Andrew C, Bullmore E (1999) Cerebral correlates of preserved cognitive skills in autism – A functional MRI study of embedded figures task performance. Brain. 122: 1305-1315

Rose F, Lincoln A, Lai Z, Ene M, Searcy Y, Bellugi U (2007) Orientation and affective expression effects on face recognition in Williams syndrome and autism. Journal of Autism and Development Disorders. 37: 513-522

Rouse H, Donnelly N, Hadwin JA, Brown T (2004) Do children with autism perceive second-order relational features? The case of the Thatcher illusion. Journal of Child Psychology and Psychiatry. 45(7):1246–1257

Russell J (1997) Autism as na executive disorder. Oxford: Oxford University Press.

Rutherford MD, Towns A (2008) Scan path differences and similarities during emotion perception in those with and without autism spectrum disorders. Journal of Autism and Development Disorders. 38: 1371-1381

Sanders J, Johnson K, Garavan H, Gill M, Gallagher L (2008) A review of neuropsychological and neuroimaging research in autistic spectrum disorders: attention, inhibition and cognitive flexibility. Research in Autism Spectrum Disorders. 2: 1-16

Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, Volkmar F,Skudlarski P, Lacadie C, Cohen D, Gore JC (2000) Abnormal Ventral Temporal Cortical Activity During Face Discrimination Among Individuals With Autism and Asperger Syndrome. Arch Gen Psychiatry. 57:331-340

Shah A, Frith U (1993) Why do autistic individuals show superior performance on the block design task? J Child Psychol Psychiatry. 34(8):1351-64

Sheppard E, Ropar D, Mitchell P (2009) Perceiving the impossible: How individuals with autism copy paradoxical figures. Autism. 13(4):435-452.

Simmons DR, McKay L, McAleer P, Toal E, Robertson A, Pollick FE (2007) Neural noise and autism spectrum disorders. Perception. 36. EVCP abstract supplement.

Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P, Polick FE (2009) Vision in autism spectrum disorders. Vision Research. 49: 2705-2739.

Sokhadze E, Baruth J, Tasman A, Sears L, Mathai G, El-Baz A, Casanova MF (2009) Event-related potential study of novelty processing abnormalities in autism. Appl Psychophysiol Biofeedback. 34(1):37-51.

Spencer J, O'Brien J, Riggs K, Braddick O, Atkinson J, Wattam-Bell J (2000)Motion processing in autism: evidence for a dorsal stream deficiency. Neuroreport. 11(12):2765-2767

Steyaert J, De La Marche W (2008) What’s new in autism? European Journal of Pediatrics. 167:1091–1101

Sundaram SK, Kumar A, Makki MI, Behen ME, Chugani HT, Chugani DC (2008) Diffusion tensor imaging of frontal lobe in autism spectrum disorder. Cereb Cortex. 18(11):2659-65.

Tsermentseli S, O'Brien J, Spencer J (2008) Comparison of form and motion coherence processing in autism spectrum disorders and dyslexia. J Autism Dev Disord. 38:1201-1210

van Asselen M, Almeida I, Andre R, Januário C, Gonçalves AF, Castelo-Branco M (2009b) The role of the basal ganglia in implicit contextual learning: a study of Parkinson's disease.Neuropsychologia. 47(5):1269-73

van Asselen M, Castelo-Branco M (2009a) The role of peripheral vision in implicit contextual cuing. Atten Percept Psychophys. 71(1):76-81.

Vandenbourke M, Scholte H, van Engeland H, Lame V, Kemner C (2008) Coherent versus component motion perception in autism spectrum disorder. J Autism Dev Disord. 38:941-949

Villalobos M, Mizuno A, Dahl B, Kemmotsu N, Müller RA (2005) Reduced functional connectivity V1 and inferior frontal cortex associated with visuomotor performance in autism. Neuroimage. 25:916-925

Walter E, Dassonville P, Bochsler T (2009) A specific autistic trait that modulates illusion susceptibility. J Autism Dev Disord. 39(2):339-49

Webb SJ, Dawson G, Bernier R, Panagiotides H (2006) ERP evidence of atypical face processing in young children with autism.J Autism Dev Disord. 36(7):881-90